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CLAUDE BERNARD IN THE LIGHT OF MODERN SCIENCE *

(ESSENCE, REVISION AND NEW FOUNDATIONS OF THE EXPERIMENTAL METHOD)

W. RIESE

"En effet, si l'expérimentateur doit soumettre ses idées au critérium des faits, je n'admets pas qu'il doive y soumettre sa raison; car alors, il éteindrait le flambeau de son seul critérium intérieur, et il tomberait nécessairement dans le domaine de l'indéterminable, c'est à dire de l'occulte et du merveilleux."

(Claude Bernard, Introduction à l'étude de la médecine expérimentale, Paris, 1865, p. 313)

History and Analysis of the Experimental Method of Claude Bernard

The introduction into the study of experimental medicine by Claude Bernard, purest and most classical product of French physiology, is devoted to the problem of causality in biology.[1] This work contains a vigorous polemic element aimed at the vitalistic doctrine and indeterminism which is an integral part of this doctrine. It is a well known fact that the vitalists at the beginning of the nineteenth century emphasized the uncertainty of vital phenomena.

* In memoriam Jean PERRIN.

No doubt, this uncertainty exists, but it led them erroneously to doubt the invariability of the *laws* ruling vital phenomena. *It is to Claude Bernard's historical credit to have reestablished causality in biology.* Although he claims this law to be the indispensable basis of experimental physiology, he admits the possibility of discordant or even contradictory results. However, instead of joining the vitalists in denying completely the determinism of vital phenomena, he attributes this uncertainty to insufficient knowledge of experimental conditions. Conditions are different if a phenomenon appears only once under definite conditions and differs in later apparently identical experiments. Mastery of the phenomena is gained with perfect knowledge of experimental conditions. There is hardly any scientific publication of the second half of the nineteenth century and of our time that does not bear witness to the triumphant march of the experimental method. This method unfolds the revolutionary effect of a searching and conquering genius rising up against the domination of dogmatism and self-satisfied speculation. It is a most inspiring and significant historical fact that it was *experimental* results which led a contemporary scientist and others after him to revive vitalistic ideas. I mean the famous experimentation made by H. Driesch who, after having divided the egg of echinoidea, saw two complete although reduced organisms being regenerated. The significance of this experiment for a complete understanding of the behavior an organism shows under normal and pathological conditions, has been stressed by K. Goldstein. Since the days of this experiment the idea of an organism as a *directed* whole has been forced upon us again; this whole striving for its actualization even under the absurd conditions sometimes realized in modern experimental embryology. This opened the road towards *synthesis* in medicine, degenerating sometimes, it is true, in empty slogans, but revealing nevertheless the compelling needs of a whole generation. In Claude Bernard's work we find already the first enunciation of this holistic doctrine,[2] but the experimental method is *analytic* in nature. Is it necessary now to go all the way back? Is it necessary to yield once more to vitalistic indeterminism? The problem is to know whether the experimental method is compatible with the contemporary views of the nature of the organism.

According to the principle of determinism of Claude Bernard, the identical effect must follow identical conditions. However, the problem is to know whether in a directed whole identical conditions can be realized a second time. The idea of a directed whole comprises that of a permanent evolution, for, as long as life lasts, the directing idea is at work and the organism tends towards its definite goal, i. e. the total fulfillment of its functions: "a living body . . . has ceaseless motions, an organic evolution, apparently spontaneous and constant. To this permanent and internal evolution the perpetual change of external conditions must be added. Observation in itself comprises a changing element. It is well known that this fact plays an important role in modern atomic physics. It was enunciated for the first time by Kant who in his preface to the first principles of metaphysics of natural science made the profound remark that an individual is modified by the very fact of being submitted to observation.

The permanent evolution of the organism as well as the perpetual changes of external conditions have not escaped the incorruptible perspicacity of Claude Bernard. In a previous article on the same subject [3] I quoted from the writings of the eminent physiologist numerous passages speaking in favour of this view. One animal can never be fully compared to another and the same animal cannot be compared to itself at various times of examination. The idea of an *individuality* of causes is expressed implicitly in an invitation to the physicians of his time to study each fact in its special determinism. However, in spite of the perpetual variation of the condition of a given phenomenon, Claude Bernard postulates the constancy of effects as the indispensable scientific basis of experimental medicine. He is not satisfied with the constancy of the *principle* but claims the constancy of *manifestations*. In other words, what he requires from reason, "torch of the only interior criterium of the experimenter," he requires also from the material phenomena, being afraid that sacrifice of the constancy of the effects should be succeeded by a sacrifice of the principle (vain fear, much the more, as in so called negative cases his own method suggests the search for the determining factors of an unexpected result, i. e. he himself refers the investigator to the principle as the last rational criterium). Thus the acuity

of our problem increases markedly. How can determinism as the fundamental principle of the experimental method be saved in spite of the permanent changes of the organism? How will Claude Bernard succeed in maintaining the constancy of effects in spite of the perpetual variation of the organism and its environment? He succeeds in two ways:

1. *By repudiating the spontaneity of living beings* Claude Bernard paves the way for a complete mastery of vital phenomena provided their exclusively physico-chemical determinism be known. Though admitting a vital and creative influence throughout the life time of the living being, he pretends nevertheless that the once created and organized living matter can be treated as if isolated from the organizing factor, left to the physico-chemical forces and studied as such, the first cause no longer interfering. I consider the passages devoted to a rational interpretation of this first cause, the " directive idea " to be the profoundest of his whole work. There Claude Bernard resists dogmatic metaphysics and his critical sense unfolds all its vigour. He refuses to admit any kind of " vital force " or ontological entity endowed with a concrete existence but upon which the physiologist cannot act. To this vitalistic and dogmatic doctrine, to this " lazy doctrine," discharging the investigator of his task and his duty to search for the causes of a given phenomenon, he opposes an interpretation which, while admitting the organized and harmonious character of vital phenomena, does not however consider them to be the effects of a substantial and mysterious entity. Accordingly he considers the initial cause as a *" rational law of the mind,"* rather than a law of physiology. It is *" the idea of the unity embracing the succession of all the morphological and chemical changes accomplished by the germ from the origin to the end of life."* [4] Being just an idea, it springs from the interpreting mind and not from nature: *" Having in himself the type of the final cause, man has been driven to conceive it outside of himself."* The error of the vitalists denying determinism and attributing vital phenomena to the spontaneous, efficient and so to say voluntary and free action of an immaterial principle, consists thus in the transforming of " metaphors " into substantial entities.[5] Let us thus start with Claude Bernard's interpretation of the initial cause (final cause, directive idea, organizing

factor) as of the idea of unity. But then, this unity realizes itself throughout all vital manifestations, even more, it is nothing but a rational formula of life. Subsequently, the responsible factor of this unity, conceived always on the model of a law of the mind, can never be omitted in any analysis of the factors cooperating in a given effect. This will be readily admitted for the so called higher, especially the psychical functions which are interpreted at the service of a goal or a plan, but at first approach it is difficult to realize the necessity or even the possibility of referring to this factor in the explication of physiological experiments. And yet, L. Lapicque,[6] eminent representative of modern experimental physiology, was induced quite recently to introduce into the interpretation of his results (variations of the chronaxies of the motor nerve) a factor realizing the unity of the organism. It is true that Claude Bernard's polemic task of refuting dogmatic vitalism and its constituent element, i. e. a vital force, as a substantial and metaphysical entity, has led Claude Bernard to eliminate definitely any intervention of this mysterious factor from the whole of determining factors. However, once this was accomplished and the *critical* formula of this principle was found, Claude Bernard could have admitted the permanent intervention of a factor no longer conceived as an ontological entity but called forth solely as an interpreting principle conceived as analogous to our faculty of acting according to aims. Indeed, the physiologist cannot act upon a principle having no concrete existence, but failing to introduce it we cannot but arrive at a fragmentary interpretation of the organism. Briefly, we are no longer concerned with discussing the *intervention* of a force in the phenomena of life, but rather with the *introduction* of a principle into the rational interpretation of vital phenomena. The efforts of the British neurophysiologists (Hughlings Jackson,[7] Ch. Sherrington,[8] H. Head [9]) were devoted to the study of the same principle and of its manifestations in experimental and pathological conditions. The realization of the unity of the organism by the cooperation of all its parts in all its reactions may be considered as the rational formula of the principle of *integration.*[10] The task of linking the organismic or integrative factors with the determinism of vital phenomena was left to the generation which succeeded Claude Bernard. It is the direct and logical continuation

of the work of the great French physiologist and the definite expression of the experimental method. Integration, i. e. the unity of the organism cannot be realized unless the principle of integration is conceived on the model of a law (of mind) inherent to and present in all members of an organized whole. Or, to yield to a vitalistic manner of speaking, the integrative factor is proper to all parts. This *universal* presence of the whole in all its parts, the nature of which is unknown and which cannot be localized, does not permit of a separation of the organizing factor from the organized product. With respect to this factor *the organism is built on the model of absolute equality of all its parts*,[11] all of them being trustees of the whole, i. e. on the model of a republic of mature citizens: " The physiologist is inclined to acknowledge a harmonious and preestablished finality in an organized body all the partial acts of which are interdependent and mutually generative " (Claude Bernard). Thus it seems impossible to study the science of life and to isolate at the same time the organizing principle from the organized being (or from their fragments) under observation or experimentation. However, this principle, in so far as it is conceived as analogous to a coordinating and unifying factor, is a *determining* factor and if this very factor is considered as translating in a rational way the " spontaneity " of living beings, then this latter quality is compatible with determinism and is indeed no longer a *lawless* spontaneity. *The solution presented here is the synthesis of the reasonable elements of vitalism and the experimental method of Claude Bernard; it recognizes the totality and unity of the organism but makes them at the same time determining factors.*

2. In rejecting the spontaneity of living beings as an explaining principle of vital phenomena on which the physiologist can act, Claude Bernard intended to render just these phenomena accessible to the experimenter. His *classification of causes* helps him to establish the constancy of effects. Indeed, according to this eminent physiologist, it is the *proximate* cause which is responsible for the appearance of a given phenomenon, and as soon as one disposes of the proximate cause one disposes of the phenomenon. The proximate cause is called " condition of existence " of a given phenomenon, or " determining cause " or " essential cause " and even

"unique cause." The problem of knowing how great a number of observations justifies such a very seductive classification of causes is a statistical one and does not affect the principle of the legitimacy of a hierarchy of causes itself. But what would be the legitimate reasons for attributing to the proximate cause a predominant role with respect to the others? What would be the *objective* criteria compelling us to consider in general the final link rather than the first one as the essential one? There are none. As soon as the existence of a series of conditions is acknowledged (and referring to a proximate cause at least a second one, its antagonist, the remote cause is admitted) the role of each member of the series is determined solely by its relation to the others. The nature of this relation however is unknown. The doctrine of the proximate cause has thus but a pragmatic value. It cannot warrant in principle the constancy of effects. Accordingly, the latter could not be considered a solid foundation of medicine as a science. In fact, there is but one: *the constancy of the principle*, obliging us to acknowledge the determinism of phenomena even if they may have appeared but once. *Indeed the fact of an event having occurred but once does not imply any doubt of its determinism.* All reactions of a living being must be regarded as a chapter of natural history and nobody expects to see strictly identical phenomena reappear in a biography. If the determinism is to be made to reappear a second time, an *experiment by reasoning* is to be made. Thus it is once more by the experimental method that the investigator succeeds in the reconstruction of phenomena starting from their causes. In biology causality is always an individual one and the search for the causes must refer to the *method of analogies*: among the conceivable causes those are chosen which can be considered as causes according to previous experience. The reconstruction of a given phenomenon by reasoning leads to a greater evidence of its causality, just as the reconstruction of its material conditions.

Rational Interpretation of Experimentation

The experimental method of Claude Bernard presupposes the constancy of effects. After having reestablished the spontaneity of living beings (although only as *analogous* to a "directive idea") and

after having rejected any classification of causes in accordance with *objective* criteria, the constancy of effects no longer exists.[12] However, nobody would deny the fact that there is in experimental medicine an impressive whole of results the experimenter can reproduce at will, due therefore to a practically realized constancy of effects. *How can this relative constancy of effects in spite of the perpetual evolution of the organism and its conditions be explained?* Constancy of effects is an element proper to mechanical causality. Thus the problem of knowing the reason and limits of the constancy of effects is traced back to the problem of knowing the relationship between mechanical causality and biological (or "final" or even "ideal") causality such as exists in an organism. Claude Bernard has violently attacked the vitalistic doctrine according to which a vital force is in opposition to physico-chemical forces or "ceaselessly at war" with them. Critique and rejection of this doctrine mark a decisive element in the work of Claude Bernard. To this doctrine the great physiologist opposes the ideas of life being due to creation and to a "directing cause" [13] and of a created organism as a machine functioning in virtue of the properties of its constituent elements and under the influence of the physico-chemical conditions acting upon these elements. These latter indeed express the mechanical factor in the causality of an organism and must be considered *as at the service* of the organizing principle or as the "executive cause" of the vital phenomena. But is it possible to trace once and for all a demarcation line beyond which mechanical causality begins and final causality ends? Again, we must be careful not to attribute an objective and concrete existence to these two causes: they are but two kinds of the same causal *thought*, precious and indispensable instrument of our interpreting reason. This same reason leads to the idea of an organism as a whole in which there is unity of organizing principle and organized product. The properties of the constituent elements of the organized machine in virtue of which the latter is able to function, comprise implicitly the "creative" or the "legislative" cause of life. In isolating the organized product from its organizing cause, we make the former a machine the organizing principle of which is outside of itself. However, a machine which organizes itself, which grows, repairs and reproduces itself, is no

longer a machine proper: its organizing principle is within itself ("in indissoluble union with the protoplasm": C. v. Monakow, [14, 15]).

Experimentation can be interpreted as an urgent and offensive problem to be solved by the organism, not belonging however to the problem comprised in the proper evolution of this organism. This evolution comprises past, present and future. But, by experimentation determining a real rupture in the individual history of the organism, the acting field is in function of the present alone. By experimentation, the part submitted to it, is quasi isolated from a *chronological* whole. From this, the following conclusion can be drawn: As at the very moment of experimentation the organism has no longer a history of its own as a decisive element of its manifestations (in this similar to inorganic matter), it may now show a behavior analogous to that of inorganic matter, this behavior expressing a generalized and elementary mechanism, in its turn at the service of the solution of that urgent and offensive task which is experimentation; this mechanism is inherent in organized matter as such. In so far as there will be in repeated experiments identity of tasks (never realized in "natural" conditions), identity of conditions is realized in such a reduced organism. Constancy of effects may then appear.

The fact has to be emphasized that isolation as realized in experimentation is not just simple isolation but affects a *chronological* whole. A machine is also a whole but a whole not undergoing evolution. Therefore, isolation of one of its parts from the rest does not induce any modification in the functioning of the isolated part or the rest provided that part and rest still admit functioning (and provided that such a modification is not anticipated in the structural plan of the machine: but then there would be no more isolation proper). But in an organism the part is isolated from a whole subjected to a permanent evolution in which, as long as integrity is saved, all the parts participate and cooperate. This universal cooperation of the parts is guaranteed by the organogenic relation of each part to all the others and to the whole. But it is precisely this organogenic relation which is interrupted by isolation depriving the isolated part of the permanent and organogenic influence of all the others and withdrawing from these latter the organogenic influence of the iso-

lated part. This latter fact explains the functional modification of the rest following the isolation of one of the parts. And so comes up the idea of an experimental research devoted not only to the study of the function of the isolated part but also to that of the rest. Indeed, the careful examination of the persistent or "positive" functions (Hughlings Jackson) has opened the way to a deeper understanding of the patient than that based exclusively on the analysis of deficient functions. I want to make it clear that reciprocal and organogenic causality is the principle of a rational interpretation of experimentation. However, in spite of the fact that in experimentation the field of action is in function of the present alone, neither past nor future can be eliminated entirely, organs and functions being the final results of an evolution and being formed in anticipation of a total realization of their possibilities, i. e. of the future. Since the days of Claude Bernard and his experimental method the (clinical) history of an animal submitted to experimentation is considered as an important element contributing to the effect. In experimentation and disease and in spite of the appearance of the contrary, the organism, as long as it exists as such, always remains an *integrated* whole. It cannot pass from an integrated state to a non-integrated state; it cannot pass either from one *degree* of integration to another, integration as unity not admitting of fragmentation. The organism may well pass from one *type* of integration to another. With regard to the "goal," i. e. the full realization of the functions of the organism, one type of integration may perhaps be considered as inferior to another and in so far the level of integration is lowered in experimentation and disease (and still we conceive the hierarchy of these levels on the model of human values, thus introducing factors which are not intrinsic elements of natural science). But, at any rate, as long as there is life and organism, a whole is realized. Generally speaking, an experimental result (or a disease) still reveals the effort of the organism (*molimina naturae*) to solve the given task in such a way that conservation and welfare of the organism is secured in the given conditions and in the future.

Summary

Determinism of vital phenomena is the essential element of the experimental method of Claude Bernard. Although the vitalistic

indeterminism is compatible neither with this method nor with a rational study of vital phenomena, a directing principle has to be introduced into the interpretation of the organism. This principle, however, must not be considered to be a " vital force " i. e. a metaphysical entity but a principle of interpretation belonging to reason and not to nature as to a whole of objective and concrete phenomena. This principle might be defined as the principle of integration achieving the totality and the unity of the organism by way of the cooperation of all of its elements endowed with the organizing principle. Far from being the opposite of a determining factor, this principle in itself is conceived on the model of causality. Constancy of effects is not a necessary element of the experimental method and of the determinism of vital phenomena. In biology causality is always an individual one and the method of reconstructing in mind a fact having occurred but once still means the experimental method. The relative constancy of effects is explained by the fact that in experimentation the organism is isolated from its own evolution, reduced to the present only and thus assimilated to inorganic matter. Nevertheless it remains always an integrated whole and the experimental result still uncovers the effort of the organism (*molimina naturae*) to maintain its welfare under the given conditions and in the future.

References, Quotations and Addenda

[1] " La méthode expérimentale a pour but de trouver le déterminisme ou la cause prochaine des phénomènes de la nature. Le principe sur lequel repose cette méthode est la *certitude* qu'un déterminisme existe, son procédé de recherches est le *doute* philosophique; son critérium est l'*expérience*. En d'autres termes, le savant croit d'une manière absolue à l'existence du déterminisme qu'il cherche, mais il doute toujours de l'avoir trouvé. C'est pour cela qu'il est sans cesse obligé de s'en référer à l'expérience. La méthode expérimentale n'est que l'expression de la marche naturelle de l'esprit humain allant à la recherche des vérités scientifiques qui sont hors de nous. Chaque homme se fait de prime abord des idées sur ce qu'il voit, et il est porté à interpréter les phénomènes de la nature par anticipation avant de les connaitre par expérience. Cette tendance est spontanée; une idée préconçue a toujours été et sera toujours le premier élan d'un esprit investigateur. La méthode expérimentale a pour objet de transformer cette conception *a priori*, fondée sur une intuition ou un sentiment vague des choses, en une interprétation *a posteriori*, établie sur l'étude expérimentale des phénomènes. C'est pourquoi on a aussi appelé la méthode expérimentale *méthode a posteriori*." (La Science Expérimentale, Paris, 1878, p. 78/79.)

[2] " . . . s'il est possible de disséquer toutes les parties d'un cadavre, de les isoler pour les étudier dans leur structure, leur forme et leurs rapports, il n'en est plus de même pendant la vie, où toutes les parties à la fois concourent simultanément à un but commun. Un organe ne vit pas par lui-même, on pourrait souvent dire qu'il n'existe pas anatomiquement, car la délimitation qu'on en a faite, à ce point de vue, est quelquefois purement arbitraire. Ce qui vit, ce qui existe, c'est l'ensemble, et si l'on étudie isolément les unes après les autres toutes les pièces d'un mécanisme quelconque, on n'a pas l'idée de la manière dont il marche. De même, en procédant anatomiquement, on démonte l'organisme mais on n'en saisit pas l'ensemble. Cet ensemble ne peut se voir que lorsque les organes sont en mouvement." (Leçons de Physiologie expérimentale appliquée à la médecine, Paris, 1856, pp. 15/16, tome deuxième.)

" Si, à l'aide de l'analyse expérimentale, on décompose l'organisme vivant en isolant ses diverses parties, ce n'est point pour les concevoir séparément. Quand on veut donner à la propriété physiologique d'un organe ou d'un tissu, toute sa valeur et sa véritable signification, il faut toujours le rapporter à l'organisme, et ne tirer de conclusion sur elle que relativement à ses effets dans l'ensemble organisé. Il faut reconnaitre en un mot que le déterminisme dans les phénomènes de la vie est non seulement un déterminisme très complexe, mais que c'est en même temps un déterminisme harmoniquement subordonné. Les phénomènes physiologiques, si compliqués chez les animaux élevés sont constitués par une série de phénomènes plus simples qui s'engendrent les uns les autres en s'associant ou se continuant vers un but final commun." (La Science Expérimentale, Paris 1878, p. 69/70.)

[3] Riese, W.: Le Déterminisme de Claude Bernard et ses Rapports avec la Neurologie Contemporaine. L'Encéphale, *29*: 661-675, 1934;

Le Problème de la Causalité dans la Névrose Traumatique. Archives Suisses de Neurol. et de Psychiatrie, *41*: 410-422, 1938.

[4] " En disant que la vie est l'idée directrice ou la *force évolutive* de l'être, nous exprimons simplement l'idée d'une unité dans la succession de tous les changements morphologiques et chimiques accomplis par le germe depuis l'origine jusqu'à la fin de la vie. Notre esprit saisit cette unité comme une conception qui s'impose à lui, et il l'explique par une force; mais l'erreur serait de croire que cette force métaphysique est active à la façon d'une force physique. Cette conception ne sort pas du domaine intellectuel pour venir réagir sur les phénomènes pour l'explication desquels l'esprit l'a créée; quoique émanée du monde physique, elle n'a pas d'effet rétroactif sur lui." (La Science Expérimentale, Paris, 1878, p. 210/11.)

[5] The view here presented that Claude Bernard adopted the vital force only as a principle of interpretation is also to be found in a paper read by Henri Bergson at the Collège de France, December 30, 1913, at the anniversary of Claude Bernard. (Bull. Inst. Hist. Med. 4: 15-21, 1936.) I interpret the above quoted passages of Claude Bernard in the light of the " Copernican method " of Kant according to which the world, instead of being the center around which I turn, turns rather around myself as its intellectual center, this center being source and birthplace of the laws which regulate and harmonize an otherwise chaotic and confusing mass of perceptions. However, neither Claude Bernard nor Henri Bergson adopted this method as a systematic one in interpreting organized nature. Still another historical remark may be made pointing more directly to the history of medicine. From the following passages the conclusion can be drawn that similar views have already

been adopted by Magendie. The assumption will be admitted that in this matter Claude Bernard was inspired by the cautious and critical reasoning of his great master:

"... il est essentiel de remarquer que la sensibilité organique et la contractilité organique insensible ne tombent point sous les sens: ce sont évidemment des suppositions, des manières de concevoir, d'expliquer les phénomènes de la vie; elles n'existent point dans la réalité, et cependant il semble que personne ne doute en ce moment de leur existence. On parle des altérations qu'elles éprouvent, de la nécessité de les ramener à leur type ordinaire; on a même été jusqu'à classer les médicaments d'après leur mode d'action sur ces propriétés, et beaucoup de médecins traitent leurs malades d'après cette doctrine. Ce fondement principal de la physiologie et de la médecine est évidemment vicieux." (F. Magendie: Précis Elémentaire de Physiologie, Paris 1816, tome premier, p. 16/17.)

[6] Lapicque, L.: Sur un mécanisme nerveux impliqué dans le mouvement volontaire. Travaux du 9e congrès international de philosophie. Hermann et Cie., Paris, 1937, fasc. 9, pp. 69-76.

[7] Jackson, J. Hughlings: Selected Writings, London, Hodder and Stoughton, 1931-1932.

[8] Sherrington, Ch.: The Integrative Action of the Nervous System. New Haven and London, Yale University Press, 1906.

———: The Brain and its Mechanism. Cambridge, University Press, 1933.

———: Man on His Nature, New York, The Macmillan Company and Cambridge, England, The University Press, 1941.

[9] Head, H.: Some Principles of Neurology. Brain, *41*: 344-354, 1918.

———: Studies in Neurology, in conjunction with W. H. Rivers, Gordon Holmes, James Sherren, Theodore Thompson, George Riddoch. London, H. Trowde and Hodder and Stoughton, 1920.

[10] Riese, W.: Critique et Interprétation rationnelle du Principe de l'Intégration. Archives Suisses de Neur. et de Psychiatrie, *44*: 313-319, 1939.

———: The Principle of Integration. Journ. of Nervous and Mental Disease, *96*: 296-312, 1942.

———: The Principle of Evolution of Nervous Function. Journ. of Nervous and Mental Disease, *98*: 255-266, 1943.

[11] Although R. Virchow in 1871 already rejected the doctrine of the "neurists" attributing to the central nervous system a permanent chief position among the other organs of the organism, modern physiologists and neurologists still maintain the same doctrine. According to traditional views the following functions are ascribed to the central nervous system: Integration, coordination, regulation, control, subordination, adaptation, adjustment, selection and orientation. Concerning the problem here raised the views of Claude Bernard are somewhat contradictory. Though he considers the brain as "the organ of intelligence just as the heart is the organ of circulation and the larynx that of the voice," thus denying to the brain any exceptional place in the organism, he nevertheless defines intelligence as "a force harmonizing the various vital acts, regulating and adjusting them to their goal." By this latter statement a permanent chief position is attributed to the brain among all the other organs of the whole. The same idea is expressed in the following sentences: "the brain and the nervous system . . . control all the other vital actions"—"the nervous influence . . . thus embraces all the vital acts and

assures the highest rank to the organic system which is in charge of exercising it." It is obvious that all the functions called forth to justify and to determine the exceptional and permanent role of the brain, are very general in nature and that it would be difficult to deny them to the living matter as such, regardless of the level examined. Indeed, those functions reveal only the proper qualities of living matter. Therefore, no system of the organism can be endowed with them exclusively and irrevocably. It is but the cooperation of the various systems in the realization of those fundamental mechanisms which varies according to time and circumstances. This caution should not be neglected in our attempt to attribute those functions to the nervous system.

[13] The constancy of effects has been explained by the permanent tendency of the organism towards a middle level of excitation (the exciting agents being the same). See K. Goldstein, The Organism, New York, The American Book Co.; 1939. There can be no doubt about the existence of this middle level being a quality proper for each organism and being its "adequate state," its real "nature," or its norm. However, as well as two different organisms have their different norms, so the same organism passes through different norms during its evolution. Therefore, the same excitation may determine different effects according to a given evolutionary stage, the great life periods, such as childhood, youth, maturity and senility being only selected and rather arbitrarily delimited chapters of the life history. The identity of the organism cannot be derived from physiological phenomena submitted in their turn to evolution thus to permanent variation. We maintain the identity of an organism or an individual in spite of this permanent variation because we are conscious ourselves of being always the same throughout the whole life and the perpetual psycho-physical changes inherent to this life. The identity of the organism is thus conceived as analogous to our own self, and this identity is only a *formal* and not a material one.

[14] The view that life is due to creation as to a *causa sui generis*, can be considered as a vitalistic element which Claude Bernard never gave up, in spite of his indefatigable effort to explain actual vital phenomena by their physico-chemical determinism. He therefore is neither a vitalist nor a materialist and all previous and future attempts to make him one or the other must fail. It adds scientific charm to the personality and work of Claude Bernard that he belongs to two ages. But only a critical view of life (as analogous to our faculty to act as to our *immediate* source of knowledge and action), traces of which are to be found in the work of Claude Bernard, can save us from a permanent wavering between those two dogmatic conceptions each of them becoming inevitably dissatisfying and troublesome for our mind.

[15] C. von Monakow et R. Mourge: Introduction biologique à l'étude de la neurologie et de la psycho-pathologie. Alcan, Paris, 1928.

[16] W. Riese: L'Idée de l'Homme dans la Neurologie Contemporaine. En Collaboration avec André Réquet. Alcan, Paris, 1938.

AN HISTORICAL SKETCH OF THE VALSALVA EXPERIMENT *

PERCY M. DAWSON

Science in Germany in the middle decades of the 19th century was enriched by the contributions of three famous brothers. The eldest, Ernst Heinrich Weber (1795-1878), was a physiologist and contributed much to physiology, especially to the physiology of the senses (24). Eduard Friedrich (1806-71), physician and physiologist, was in his second capacity the colleague of his elder brother Ernst. Finally there was Wilhelm Eduard (1804-91), a physicist, who shared to some extent the physiological interests of his brothers for he wrote on the mechanics of standing and of human locomotion. Our concern is with the youngest brother, Eduard Friedrich.

Beginnings

At a public meeting of the Royal Saxon Scientific Society at Leipzig, a meeting held in 1850 in honor of the King's birthday, Eduard Friedrich Weber reported a series of experiments performed upon himself which were of a most spectacular nature.

> Several years ago, I discovered and have since shown to my friends that I could interrupt at will for a moment, the beats of my heart and the pulsation of my arteries by hindering the air from entering into my chest which I was at the same time compressing; . . .
>
> The cessation of the shock of the heart is immediately accompanied by that of the auricular and ventricular sounds and of the aortic and pulmonary murmurs. One still feels three to five very feeble pulsations and then there is a sudden cessation.

As an explanation of this phenomenon Weber states that the high pressure within the thorax compresses the veins therein so that the blood cannot enter the thorax and soon the heart having nothing to pump, abates its activity. Then he continues:

> One day, when I held my breath a little longer than usual, . . . I lost consciousness. While I was in this state, my assistants noted some con-

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vulsive movements of my face; when I returned to myself I had lost the memory of what had passed and for the first moment I could not recall where I was although my pulse had become palpable. I have kept in mind to desist from thoracic compression as soon as I felt fainting coming on, and it is probable that if I should not do so, it would be dangerous for me and my life might perhaps be jeopardized.

Weber then points out that the symptoms of fainting and those of thoracic compression are so similar that they are doubtless to be attributed to the same cause, namely stoppage (*sic*) of the heart. Furthermore he points out that this compression of the chest is a familiar part of several common acts such as vomiting, coughing, sneezing, defecation, parturition and so forth.

Deeply interested in the phenomena of thoracic compression, Weber delved into the literature. In Haller's encyclopedic *Elementa*, 1757-66, he found references to Valerius Maximus and to Galen.

In the *Memorabilia* of the former, in the chapter entitled "On uncommon deaths," Valerius tells the following story: Coma, they say, was the brother of Cleon, the ringleader of the brigands. When Henna, which the brigands had held, had fallen, this Coma was led before the consul, Rupilius, and questioned about the strength and plans of the fugitives. As if considering his reply, Coma covered his face and [being seated] bent forward upon his knees. Then between the very hands of his guards and within sight of the highest power of the state, through compression of his breath he found the rest and security he desired.

"Wretched people," continues Valerius, "to whom perishing is preferable to surviving, torture themselves with timid and anxious council, inquiring by what plan they shall make their exit from life, they would sharpen a sword, mix poisons, grasp a noose, look about for immense precipices as though there were a necessity for so great preparations or so exquisite technique for breaking the feeble bond which unites the body and the spirit. Coma did none of these things but having confined his breath within his chest, found an end for himself."

The Galenic passage runs as follows: "Respiration is entirely subject to the will and depends upon the soul. This is proved by the example of a foreign slave who resolved one day in a violent fit of anger to kill himself; he stretched himself upon the ground holding

his breath and died after having remained for some time immovable and then being a little convulsed."

Another classical passage cited by Weber is the following story of Cato of Utica told by Appianus of Alexandria: As he did not find his sword in its accustomed place beside his couch, he exclaimed that he had been betrayed to the enemy by his servants. "What weapon shall I use if I am attacked in the night?" he said. When they besought him to do no violence to himself but to go to sleep without his sword, he replied still more plausibly, "Could I not strangle myself with my clothing if I wished to, or knock my brains out against the wall, or throw myself headlong to the ground, or destroy myself by holding my breath?"

As a matter of fact Cato did not end his life by "holding his breath" but the passage seems to indicate that this method of suicide was not unfamiliar to Cato and to his servants whom he was addressing.

In all of these instances death seems to have been attributed to the mere cessation of the respiration. This view prevailed at the time of Haller for the latter writes thus: "If by the effect of a strong will, one hinders the air from entering the lungs or indeed from going out, it is possible to see a strong and perfectly healthy man suddenly die. It was thus that the brigand died who was led before Augustus (*sic*) and the foreign slave of whom Galen speaks; it is also the means employed by the slaves of Angola . . . Children, who through anger or some other cause, hold their respiration may die in like manner."

Weber quotes also the well known story of the "man who could die and come to life again," which George Cheyne had told in 1734. And finally he presents several examples of conflicting current opinion (58, 78, 95).

But there was one writer whom Weber overlooked. In 1761 Morgagni published his great work, *On the seats of diseases*, and in this work included previously unpublished material of his honored master Valsalva (1666-1723). Among these literary remains is the following passage: "If the glottis be closed after a deep inspiration, and a strenuous and prolonged expiratory effort be then made, such

pressure can be exerted upon the heart and intrathoracic vessels that the movement and flow of the blood are temporarily arrested."

This passage escaped for a long time the attention of those who were working on the relation of the respiration to the circulation (93, 90, 29, 62, 99, 28). I have as yet found no reference to it prior to 1869 when it appears in Longet's textbook but by 1880 the voluntary compression of the chest with consequent modification of the circulation had become so well known as "the Valsalva experiment" that this designation could be used without comment in the best German "Handbook" of the time edited by L. Hermann.

It was therefore not the work of Valsalva but of Eduard Friedrich Weber which attracted to this field of research the attention of Einbrodt of Moscow, 1860, a former pupil of Karl Ludwig, Ernst Heinrich Weber's successor.

Since animals cannot be made to compress their own chests, a rise of intrathoracic pressure for experimental purposes is produced in them by blowing up the lungs with air. Under these circumstances Einbrodt showed a great fall of arterial pressure and proved this to be due (as Weber had suspected) to the inability of the blood to enter the thoracic cavity, so that the heart becomes depleted and its output falls. He also pointed out the changes in the heart rate, an acceleration during the effort and a great slowing following it, and pointed out that these changes depend upon the integrity of the vagus nerves of the heart. He furthermore performed experiments upon himself noting the effect by means of a sphygmograph, an instrument for recording the pulse at the wrist. And his sphygmograms, according to his interpretation, were in harmony with the results of his experiments on animals.

It would carry us too far afield to consider all the implications of Einbrodt's work. Suffice it that it had important bearings upon the so-called "pneumatic treatment" of lung diseases, which seems to have arisen and attracted considerable attention in the sixties and seventies (27, 57, 106, 98) and still retains its interest (4); that it underlay the subsequent development of our knowledge of the nervous control of respiration; and finally that it started a controversy as to the interpretation of the records obtained by the sphygmo-

graph which lasted well into the next century and would make an entertaining chapter by itself (51, 86, 53, 54, 98, 45, 44, 59, 71).

Sphygmomanometry

In the early eighties the subject of the V. was beginning to be approached from a new angle. A new technique, that of the sphygmomanometer, had been devised for determining the arterial pressure in man, and between 1876 (v. Basch, Marey) and 1905 (Korotkov) many varieties of this technique and many sorts of instruments were developed. But for some time the results were conflicting and unsatisfactory.

Meanwhile more of the practical applications of studies of the "Valsalva" had become recognized. Thus in 1899 Wolffhügel in his book entitled *On the pathogenesis of overstrain of the heart* notes that essentially similar to the results of the V. are those occurring in heavy lifting such as belongs to the occupations of quarry men, coopers, porters, furniture movers and the like. "Usually in this sort of work custom and practice enable the worker's circulation to recover, but even for the strongest and most practiced there is a limit as is seen by the cases of sudden death from cardiac paralysis." But apparently, so far, no experiments had been performed on actual lifting until McCurdy, 1901, took the matter up.

McCurdy, later medical director of Springfield College and editor of the American Physical Education Review, studied at Harvard the effect of lifting, by means of a new sphygmomanometric method (Riva Rocci, 1896). The latter consists, first, in applying pressure to the upper arm by means of an encircling bag which can be blown up to produce upon the arm any desired pressure and, second, in noting the pressure required for the obliteration of the pulse at the wrist. The lift selected was that used in the physical examinations of college students. The subject stands with bent knees; with the left hand he grasps the middle of a dynamometer handle, the ends of which rest on the front of the thighs; at the word, he extends his legs and straightens his back with all his strength. McCurdy found that during lifting the enormous arterial pressure of 200 mm. of mercury might frequently be attained. The fact of the occurrence of such a great rise in arterial pressure in exercises of strain makes clear the

reason why persons, whose arteries have become stiff and fragile whether through old age or disease, are subject to apoplectic strokes as the result of undue effort.

But, as we have seen, the arguments of Weber and the experiments of Einbrodt point to a *fall* in pressure. How can this be? The resolution of this apparent conflict is found in the work of Erich Bruck.

In 1907 Bruck, apparently ignorant of McCurdy's work, published a study of the arterial pressure during lifting and the V. He found 1, that there is at the beginning always a rapid rise in arterial pressure; 2, that invariably this rise is soon followed by a fall which usually reaches a point below the resting pressure, sometimes as low as 60 mm.; and 3, that in the majority of cases a second rise then occurs which as a rule over-steps the resting level, sometimes even surpasses the first maximum. Note that this second maximum occurs ***during*** the V.

In 1916 and 1920 came the articles of Dawson and Hodges. They used the best instruments known at the time or, for that matter, since, namely the Erlanger recording sphygmomanometer and the stethoscope applied to the artery below the encircling arm bag or "cuff" (Korotkoff). They were familiar with the work of Bruck but they failed to confirm one of his results, namely the second maximum during the effort.

The initial rise of arterial pressure obtained by them was as great as that of McCurdy (to 200 mm. Hg)—much greater than that of Bruck. The fall was as low as that of Bruck (*i. e.*, somewhere below 60 mm.). But while the subsequent rise in Bruck's experiments might reach even 200 mm., to be succeeded on cessation of the effort by a rapid fall to normal, the corresponding rise found by Dawson and Hodges rarely reached 140 mm. and was succeeded on cessation of the effort by a still greater rise, the "after fling." This after fling is so sudden and extensive that Dawson and Hodges attributed to it the same possibility as to McCurdy's rise, namely, the rupture of weakened arteries and consequent apoplectic strokes.

Later observers have shown that both of these pictures are correct for the behavior of the arterial pressure depends partly upon the way in which the V. is performed. It is only when the effort is maximal and not too long continued that the results of Dawson and Hodges are to be obtained.

In the same year, 1920, there was published in England a report of the Medical Research Council containing a section by Martin Flack describing tests of "fitness." One of the tests was called the "40 mm. test" and consisted in blowing against a mercury manometer and holding the column at 40 mm. as long as possible. The duration of the blow was noted and also the pulse rate counted throughout the duration of the effort. The test was originally devised to determine the physical condition of aviators and was used with great satisfaction by the Royal Air Force in the first World War. Of all their respiratory and circulatory tests this one proved to be the most delicate. The fit pilot usually holds out for about 66 seconds; the minimum allowed is 45 sec. If he cannot hold out for 45 sec., he is sure to be found wanting on medical grounds. During the effort the pulse either rises gradually to 96 or 108, depending upon the duration of the effort or it rises at once to 96 or 108 and remains at that level. Such behavior is "satisfactory." But a large rise of pulse rate to 132 or 144 is "unsatisfactory" and so is a pulse rate which after rising to a high level, begins to fall rapidly before the end of the effort. Besides noting the duration and the pulse rate, the answer of the subject to the question "Why did you stop?" is also recorded. There are satisfactory answers and unsatisfactory ones. The former are "I wanted more breath," "I felt like bursting"; but unsatisfactory are those in which the following symptoms are mentioned: giddiness, blurred vision, nausea, fainting or head ache.

Observations of blood pressure were not included in the regular test but nevertheless Flack and Burton, 1922, subsequently made some of these. In all cases both systolic and diastolic pressures rose steadily sometimes to a great height, e. g., at 85 sec., 178 systolic, 136 diastolic, "fit"; at 38 sec., 212 systolic, 122 diastolic, "unfit."

In these experiments the observations of the blood pressures began too late to catch the McCurdy rise. The intrathoracic pressure was never high enough to prevent the return of blood to the heart and so to cause a deep fall like that obtained by Bruck and lastly the effort continued long enough to permit a great secondary rise similar to that obtained by Bruck and probably due in large part to asphyxia.

In the titles of the articles dealing with his test the words "Valsalva" or "intrathoracic pressure" do not appear and the same is true of McCurdy's article. This is a probable explanation of the fact that these articles have not been referred to in the German bibliographies. The title of the second article of Dawson and Hodges reads "Cardiovascular reactions in the Valsalva experiment. . . ." and it is doubtless for this reason that it has not been completely overlooked but found its way into a German bibliography in 1934 (Nolte).

In 1921 began a veritable stream of articles from Germany (74). At first the most outstanding work was that of Max Bürger who reported briefly in 1921 and 1925 and at greater length in 1926.

As in the case of the English physiologists, the keynote of Bürger's work is its practicability. He wished to use the V. as a test of circulatory efficiency and so he established the following standard mode of procedure. His subjects were told to blow against a mercury manometer and to hold the column at 40-60 mm. for 20 sec. and meanwhile Bürger himself made determinations of the arterial pressure. These determinations, be it remarked in passing, began 5 sec. after the beginning of the V. and so his writings do not mention the initial (McCurdy's) rise, which he failed to observe.

On the basis of a large number of observations, Bürger advanced two novelties. The first was a three-fold division of hearts into athletic, ordinary and weak. In the first division, the arterial pressure rises throughout the V.; in the second, it falls a little and then returns promptly to rise above the initial level before the end of the V.; in the third, the fall is very great and the return to the resting level very slow and hardly completed during the V. Later observers, as we shall see, have pointed out defects in this classification.

Bürger's second contribution is his conception of the "syncopotropic" heart which has been very fruitful.

Subjects with "syncopotropic" hearts are characterized by their reaction to the V. After blowing for 15-20 sec. they collapse! With dilated, unreacting pupils and slight clonic twitching of the upper extremities, they lie unconscious. Often there is a strong outbreak of sweat. Brought to the horizontal position, the subject after half a minute reacts again to calling as one who is being aroused from a

deep sleep. Usually there is complete amnesia for what has gone before. These subjects may be competent sportsmen, but they often give a history of fainting. For example: F. K., 25 years, powerful and well built, a good turner. Two years ago he fell from the height of the giant swing without known cause. The fall was broken by the right hand cramping on the horizontal bar. On test F. K. blew against 40-60 mm. Hg and at 15 seconds his heart slowed and he collapsed with clonic spasms especially of the right arm.

Bürger and Petersen, who worked with him and later paid especial attention to the matter of swimming, came to the belief that swimming accidents may be due to the unconscious performance of the V. more frequently than is generally supposed. Doubtless they were unaware that Emmert had said much the same thing in 1802. They describe many cases more or less similar to the following. H. S., 26 years, moderate swimmer, strength and nourishment good. Five years ago while bathing in a familiar place, he suddenly sank. He regained consciousness in a hospital. Of the occurrence of the accident and its cause he knew nothing. Petersen, 1928, had him stand and blow against 50 mm. Hg. At the end of 10 sec. he collapsed with complete unconsciousness. The importance of all this is obvious not only in the testing of athletes but also in medical jurisprudence (again, as Emmert has said!)

In 1928 Bürger and his associates obtained fresh material for study, namely 81 super-athletes competing at the Olympics in Amsterdam. Of Bürger's three types of reaction that of the "weak heart" (deep fall of pressure) was wholly absent. Of the 81 hearts 78 reacted according to the "athletic type" (rise of pressure); 3 only were found of the "ordinary type" of reaction (a brief fall preceding the athletic rise). Unfortunately these 3 hearts could not be closely studied and the significance of their behavior remains uncertain. Could these subjects have been unduly nervous or overtrained at the time of the test? In general it may be stated that the heart well trained in no matter what sport, becomes promptly adapted to change of intrathoracic pressure.

Interesting is the effect of fatigue upon the reaction to the V. Before the marathon the V. causes a considerable rise of pressure but after the race this rise is less and the subsequent return to normal slower.

Between 1929 and 1932 inclusive four American insurance doctors, MacKenzie, Wells, Dewis and Ylvisaker reported upon a new combination of tests ("flarimeter") of their own devising. Incorporated in these tests was a modification of the breath-holding test like that devised by Flack but differing in three respects: 1, the pressure blown against is only 20 mm.; 2, there is a very small hole in the tubing enabling the lungs to be partly emptied before asphyxia supervenes, so that the subject is comforted by the feeling that he is accomplishing something by blowing; 3, the arterial pressure is determined throughout the effort. The pressure changes obtained in this way resemble those obtained by Bruck for the doctors' modification has changed the original breath-holding test into a very mild V.

But why, it may be asked, all this complexity in place of simple breath-holding? Because some subjects cannot be trusted to give reliable results with simple breath-holding, either because of dishonesty or because of ineptitude. But with this device they cannot draw breath without letting down the mercury and disclosing their error.

Others working in the field of sphygmomanometry were Sirakoff, 1930, and Koch, 1931, of whom the former rediscovered the McCurdy rise, and finally Csinády and Purjesz, 1940, whose observations were very extensive.

Csinády and Purjesz submitted 3,000 persons to the Bürger test. Of these cases 2,520 (84%) showed no change or a rise in pressure and were not studied further. 480 (16%) showed a fall in pressure and in 90 (3%) of these the fall is described as a "plunge."

In only 7 cases were there collapse and unconsciousness showing what Bürger had designated the syncopotropic reaction. But for those others whose fall was as great or greater than 40 mm. (6% including the "plungers") there was very little evidence of circulatory inferiority. In a few cases only could it be shown that "plunging" was a forerunner of weakness later brought out by severe strain and disappearing with rest, along with the other pathologic manifestations. So the chief contribution of these writers is to cast doubt upon the prognostic value of Bürger's classification. Bürger's method they say has the advantage of simplicity but should not be permitted to replace the X-ray and electrocardiogram.

It is interesting to compare this statement with that of recent X-ray workers who insist that their own method cannot be relied upon except in combination with the electrocardiogram and the Bürger test!

X-ray

As early as 1894 v. Criegern observed the shrinking of the heart shadow during the V. But the most vivid of these first descriptions of the fluoroscopic picture is that of Dietlin (1906), who writes as follows: "One sees . . . the heart . . . become with each contraction smaller and smaller until an alarming degree of emptiness is reached, which corresponds to an almost bloodless condition of the heart." But the heart never stops beating altogether as some, e.g., Weber, had previously surmised.

As observations multiplied it was seen that hearts differ very much in the amount of shrinking which they undergo. And this gave rise to the use of the V. for the differential diagnosis of cardiac hypertrophy and cardiac dilation. In the first the heart is stiff because of the increased thickness of the muscle forming its walls and so it does not show much diminution. While on the other hand the dilated heart of the same size as the hypertrophied heart is thin walled and readily yields under compression. (73, 26, 79)

Bürger had, as we have seen, defined his three types of heart in terms of arterial pressure. But on fluoroscopic study of the shrinkage due to the V., he had found (1926) changes corresponding to these three types. Thus his athletic heart shrinks 10%, normal heart 15% and weak heart 25%.

About this time also it was shown by Mosler and Kretschmer, 1924, that the hearts of children shrink readily during the V., that is, they behave like weak hearts in adults.

The invention of a form of X-ray movie ("X-ray kymographion") called forth an enormous amount of new experimentation with the V. (105, 31, 80, 81, 52, 41). The first effect seems to have been the multiplication of details without any fundamental advance. One of these details may however be worth mentioning: the brief dilatation of the heart at the very beginning of the V. (80). This corresponds in time to the entrance into the left side of the heart of

the extra blood squeezed out of the lungs by the thoracic compression. It is the subsequent sudden expulsion of this blood from the heart which produces the initial (McCurdy's) rise.

In 1939 Albert and Klaus presented something quite new. They had come to the conclusion that from the point of view of roentgenology the simple V. is without value. Even the difference between hypertrophy and dilatation cannot be distinguished with assurance, not to mention the diagnosis of cardiac efficiency. They therefore substituted for the simple V., the "step V." In this the subject blows against 20 mm. Hg for 10 seconds and then without drawing breath against 60 mm. for another 5 seconds. But in the judgment of Klaus and Albert even the introduction of the step V. into roentgenology is not enough to afford a reliable diagnosis. X-ray examination must be supplemented with determinations of the arterial pressure and pulse rate.

This battery of tests has not been adequately studied. Albert and Klaus themselves have so far applied it only to athletes and have omitted the determination of arterial pressure altogether.

According to the behavior of the cardiac area toward the step V., Albert and Klaus divide the hearts of athletes into four types. Here the criterion is the relation of the shrinking of the area during the first step to that during the second step or, differently stated, area during V_1 minus area at rest divided by the area during V_2 minus area during V_1.

In type I the relation is 2-3 : 1; II, 1 : 2-3; III, 1 : 1. In type IV the heart decreases during V_1 but increases during V_2.

II and III are efficient hearts; IV is rare and little understood. I is open to suspicion and to a subdivision of this type belong the syncopotropic hearts.

The X-ray kymographion used by Albert and Klaus permits one to assemble a second series of measurements, namely, the amplitude of movement of the rim of the shadow at each cardiac contraction. The significance of these movements lies in the fact that from them we may form a rough estimate of the relative amount of blood expelled from the heart at each contraction.

The observations of the pulse rate make a third series of data. In general it may be said that it is the fast hearts that are most open to suspicion. It is to this class that the syncopotropic hearts belong.

In this manner Albert and Klaus secure three sets of data. Of course the addition of arterial pressure would have been highly desirable but even without it these investigators think that a prediction can be made as to the efficiency of a given heart.

Electrocardiograph

In 1909 Kahn applied this instrument to the study of the V. His apparatus permitted him to make only short strips of record but these he studied minutely.

The work of Kahn was corroborated and materially extended by Dawson and Hodges, 1916, 1920. According to them the pulse rate quickens with the preliminary deep inspiration, decreases below normal with the beginning of the strain, then quickens gradually to a very high rate until the strain ceases. Then follows a period of extraordinary slowing and then a return to normal.

These changes they regard as compensatory reflexes tending to neutralize the changes of pressure described by them. Thus after the slight introductory acceleration (the usual accompaniment of a deep inspiration), a slowing of the pulse accompanies and tends to ameliorate the severity of the McCurdy rise of pressure, then follows the deep fall of pressure and with this the pulse rate begins to quicken, faster and faster goes the heart until the end of the compression. Then comes the after fling and with it the slowing already referred to as "extraordinary."

The electrocardiogram moreover permits comparison of the duration of the heart cycle (Q-Q′) with that of the ventricular contraction (Q-T). This proceeding shows that the acceleration of the heart is at first accomplished at the expense of the pause between beats, and that only later does the shortening of the cycle involve the shortening of the ventricular contraction. This would lead some cardiologists to infer that the changes in heart rate are due at first to action of the vagus nerves, as definitely shown for animals by Einbrodt.

Since 1920 this field has been cultivated by several investigators (38, 75, 15, 2) and at length the time seemed ripe for offering a series of criteria of fitness based upon the effects of V. upon the

electrocardiogram. So Schlomka and Lammert, 1935, on the basis of previous work on the effect of exercise, divide hearts into two classes, stronger and weaker and then on comparing these classes in respect to the V. they find that their reactions differ in the following ways: In stronger hearts, T becomes small during the V. and the ratio S : R decreases. In the weaker hearts, T remains unchanged and S : R increases. Again during the V. $\frac{Q\text{-}T}{Q\text{-}Q'}$ increases less in the strong than in the weak hearts; while after the V., it decreases less in the former than in the latter. Finally P (auricular contraction) is less likely to be dislocated in the strong hearts after the V., which shows a lesser tendency in these hearts to undesirable, if not pathological, departures from normal behavior.

Venous Pressure

It is surely a matter of common knowledge that straining causes a rise in the venous blood pressure. For this is of course only another way of saying that the veins of the neck and face become engorged with blood when we strain. Bürger measured the venous pressure and found a rise to 50 cm. of water from a resting level of 8-10 cm. Subsequently attempts were made by others (46) to correlate the rise during the V. or the rapidity of the fall afterwards with cardiac efficiency but in 1939 the last attempt still resulted in failure. (60)

The behavior of the venous blood is however a very important factor in the V. Bruck, 1907, first suggested that the second rise of pressure obtained by him during the V. might be due to the inflow of blood from the abdominal cavity. But it remained for Nordenfeld, 1934, to make a careful study of the question. His method consisted in placing three balloons attached to 3 recording manometers in the esophagus, stomach and rectum respectively. It can readily be guessed that the difference in pressure between the cavity of the thorax and that of the abdomen during the V. will depend upon what the diaphragm is doing. If the diaphragm be relaxed it will play no role as a division wall between these two cavities so that the pressure is the same in both. If the diaphragm contracts it may raise the pressure in the abdominal cavity above that in the thoracic cavity and so force a stream of venous blood from the abdominal

cavity into the thoracic cavity and the heart. It is probable that in the results obtained by Nordenfeld, we have suggestions for the answers of a number of questions. Although more observations are required, one might surmise that the response of a given subject to the V. depends not only upon the action of his heart but upon factors controlling the return of blood through the abdominal veins to the heart. Here might be found additional reasons for the discrepancies between the results of various writers.

Central Nervous System

Since 1920 several studies have been made of the effect of the V. on the central nervous system. Already the clinicians, e. g., Quincke, 1906, had found that, when a coarse hypodermic needle connected with a manometer is stuck into the spinal canal (lumbar puncture), the pressure of the cerebro-spinal fluid rises when the patient coughs. But it was Bürger, 1921, who first made measurements during the V. and found a rise from a resting value of 12 cm. to 100 cm. H_2O. Obviously the central nervous system, i. e., brain and spinal cord, does not escape the action of the high intrathoracic pressure and so deserves further study.

This brings me to an interesting tale: Once upon a time some students of the University of Chicago came to the department of physiology asking for an explanation of the following phenomenon. If A, standing behind B, throws his arms about B and while compressing his chest raises him from the ground, B presently loses consciousness. This maneuver is employed in many localities for the purpose of entertaining the onlookers at fraternity initiations and other social gatherings. To such a question the obvious answer would be that the maneuver is a form of V., that moreover, when the V. is performed in this manner, the body being immobilized in the erect posture, the chance of any adequate compensation by means of increasing the intra-abdominal pressure would be very small indeed.

To Johnson and Luckhardt of the Chicago staff the performance seemed to be outrageously risky. Then stimulated by this incident they investigated (1928) the effect of raising the intrathoracic pressure in dogs upon the activity of the central nervous system in these animals.

The test chosen to indicate the condition of the central nervous system was the knee jerk. On blowing up the lungs of dogs, the knee jerk is at first improved (doubtless because of the cutting off of inhibitory impulses from the higher, more sensitive centers). But soon the more resistant spinal cord becomes affected and the knee jerk is abolished entirely. On deflation of the lungs, the knee jerk recovers but does so only very slowly, recovery being only partial at the end of fifteen minutes.

Optical Registration

I come now to a method which may be described as "multiple, simultaneous, optical registration." This method involves placing tiny mirrors on various arteries and simultaneously recording their movements by photographing reflected beams of light.

This technique has opened up a whole chapter in the dynamics of the circulation. For one thing it permits accurate comparison in respect to time of the pulse records made at different distances from the heart and yields thereby values from which the velocity of the pulse wave may be determined as it travels from the heart away through the arteries.

This velocity increases more and more as the walls of the arteries become stretched tighter and tighter by any rise in the pressure of the blood within them, e. g., during exercise. Conversely the velocity falls if the arterial pressure falls and thus relaxes the vessel walls, e. g., in sleep. So in persons with hypertension the velocity is continually high and it is correspondingly low in cases of hypotension.

The same graphic records that show the pulse velocity show also the time relations and forms of the secondary reflected waves in the blood stream which likewise have a hemodynamic significance (34, 9).

In 1932 Böger and then in 1937 Wezler and Knebel applied this technique to the study of the V. The more recent of these workers soon found it necessary to distinguish between two categories of arteries, viz., the intrathoracic, i. e., the aorta and its immediate large branches, and the extrathoracic, e. g., the arteries of the arm. In the case of the former (intrathoracic), the action of the V. is to

compress them from without and thereby relax their walls and slow down the velocity of the pulse wave.

Now it happens that the aorta is normally not merely a large channel for the blood to run through. It is also a "wind chest." With every heart beat the aorta dilates and, during the pauses between beats the aorta contracts elastically and squeezes the blood along toward the smaller arteries. It is this wind chest action which gives us normally a high diastolic pressure, say 70 mm. Hg. Naturally the V. by relaxing the aortic walls greatly reduces this "wind chest" action.

Would it not be interesting to surmise what would happen if we could protect the aorta from compression during the V.? Presumably if the aorta were a rigid tube, the velocity of the pulse wave would be high and unaffected by the V. Fortunately we do not need to content ourselves with surmises. Steinman and Bucher, 1940, have studied persons with arterial sclerosis whose aortic walls were so impregnated with lime salts that the condition could be observed with the fluoroscope and in these persons the velocity of the pulse wave behaved as predicted: rapid during rest and unaffected by the V.

But our investigators went further. In their study of the pathological hearts they found that they could detect by means of the V. the early stages of sclerosis before the depositing of lime salts had begun. And what makes the account credible, some of the arteries of the patients were examined post-mortem.

Let us return to Wezler and Knebel. These workers found that, in contrast to the intrathoracic vessels, the vessels which lie outside of the thoracic cavity, e. g., those of the arm, escape this action of external compression and in them during the V. the velocity of the pulse wave is as high or higher than during rest. And from the persistence of high velocity we conclude that the arterial pressure in the arm does not fall during the V. under the conditions which prevail in these experiments.

Enumerating the chief items furnished by this method, some of which have already been referred to, we have: 1, reduction of the wind chest action of the aorta; 2, reduction of the heart's output per minute; 3, powerful constriction of the small arteries of the arm

thus rendering difficult the passage of blood through them, and 4, small changes in the arterial pressure of the arm.

The changes of arterial pressure consist in a moderate rise followed by a fall. The latter compared with the fall described by other investigators, e. g., Bruck, is trivial, amounting to only a few mm. below the resting level. After this the pressure remain constant or rises somewhat.

That the arterial pressure in the arm may not fall with decreases of the cardiac output per min. is explained as follows: the V. cannot be strenuous in these experiments otherwise the pulses would become too small to be recorded; with a mild V. the blood can still pass by the veins to the heart though in reduced quantities; the corresponding decrease of inflow into the large arteries from the heart would be more or less offset by constriction of the small arteries mentioned above which would prevent the exit of the blood from these large arteries through the small ones toward the tissues; and this compensation for the reduced cardiac output would be partial or complete or there might be overcompensation according to the degree of constriction occurring in these small arteries.

In passing it may be noted that constriction of the arteries of the hand during the V. was demonstrated as long ago as 1879 by a method (plethysmographic) which I shall refrain from discussing (7, 77, 94, 43).

The result of Wezler and Knebel in respect to the pressure in the artery of the arm is similar to that of Hamilton, Woodbury and Harper, 1936, who boldly thrusting a hypodermic needle into the brachial artery, have measured the arterial pressure in the most direct manner possible and failed to find a fall during the V.

Oxygen Supply

In 1938 a new note was introduced into the discussion. Karl Matthes then reported a study of the oxygen content of the blood during the V. This author thinks that the element of asphyxia in the V. has never received adequate attention. The fall of oxygen in the blood depends not only upon the effect of the intrathoracic pressure upon the circulation but also upon the demands made by the

organs upon the oxygen of the blood. Thus during the Bürger test there may be no change observable in the oxygen content of the blood. But on the other hand simple voluntary holding of the breath during maximum work will produce unconsciousness and before actual fainting there may be failure of judgment due to lack of oxygen. The combination of the V. with heavy work is of course still more serious and it is important also whether the V. has been preceded by effort as when a man swims vigorously before diving.

Paroxysmal Tachycardia

Because of the present interest in the V. in the treatment of paroxysmal tachycardia, a brief note on the early work in this field seems desirable. This work is summed up in two articles by Giovanni Galli. To Galli the suspicion with which many persons regarded the clinical use of the V., seemed unjustified. Luciani called it "dangerous"; Wenkebach, "venturesome." Galli used it freely without untoward results. August Hoffmann had done the same. Galli reports reducing the pulse rate from 210 to 60 by means of the V. Both he and Hoffmann had found that such attacks could be brought on in susceptible persons and Galli's curves show changes of rate from 60 to 195 and from 100 to 200.

Such is the history of the Valsalva experiment. It is a long history and even in the simplified form in which I have presented it, it is seen to be intricate, touching upon many fields and appealing to varied interests. We have travelled a long way since the days of the Roman Empire and many brilliant minds have been interested in the journey. But nevertheless the present status of the V. is far from satisfactory.

Indeed were I asked to tell how the work on the Valsalva can be utilized to human advantage, I am afraid that the question would be almost as embarrassing to me as the questions of Rupilius were to Coma.

Only the historian can fully realize the relative unfruitfulness of the vast amount of experimentation and of study devoted to the Valsalva. And the reason for this state of things is not far to seek. For when many different persons, often with but meager acquaint-

ance with earlier publications, experiment with many totally different techniques usually upon different groups of subjects, how can the results be otherwise than conflicting and bewildering!

The remedy for all this would seem to be better collective planning. If it is imperative, as it seems to be, to provide a situation, in which *all* the various instruments and techniques can be applied to the *same* subjects as nearly as possible at the *same* time and in which the same series of experiments can be carried out by *different* teams of observers, then we must resort to some such procedure as obtains in certain institutes devoted, for example, to cancer research. For in such institutes problems are simultaneously attacked from a variety of angles by persons trained in a variety of disciplines and the attack is cooperatively planned.

I do not envisage a *building* devoted to the Valsalva but rather a temporary organization of people working in close cooperation. This idea is not new either in theory or in practice. But it is presented with emphasis at the present time because it seems to be just this procedure which is demanded for the advancement of our knowledge of this very ancient Valsalva experiment.

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AN HISTORICAL INTRODUCTION TO THE PHYSIOLOGY OF ANOXIA

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Aristotle believed that it was impossible for man to live at the top of Mount Olympus without a wet sponge, by the use of which, he could "respire in that air, otherwise too thin for respiration" (7, p. 357). This is, indeed, a remarkable observation, although it is difficult to appreciate the value of a wet sponge under these conditions. It is, nevertheless, one of the earliest reports of the deleterious effects of low atmospheric pressure.

Eight years before the birth of William Harvey, Father Joseph de Acosta crossed the Pariacaca mountain in Peru, at a height of approximately 14,000 feet. Seven years later he returned to his native Spain, and in 1588 his book entitled, *The natural and moral history of the Indies*, was published, (1) wherein he recorded a detailed description of his travels in the New World. One of his observations attracted the attention of Boyle in the 17th, of Cigna in the 18th, and of Bert in the 19th century, and anyone attempting to investigate physiological problems involving low atmospheric pressure cannot fail immediately to be thrilled by the sagacity, and striking dogmatism of the following quotation: *

> I therefore persuade my selfe that the element of the aire is there so subtil and delicate, that it is not proportional with the breathing of man, which requires a more grosse and temperate aire, and I believe it is the cause that doth so much alter the stomacke and trouble all disposition (1, p. 131).

This passage is all the more remarkable when one realizes that the prevailing conception of respiration remained that of Galen and Aristotle, who taught that the air which passed into the lungs served merely to cool the heart. A century was to elapse before the publi-

* Only through a familiarity with the exact phraseology employed by these early investigators can one begin to appreciate the immensity of the problems with which they labored, and the charm and ingenuity of their explanations. Accordingly, throughout this paper, the more important observations are presented in the words of the scientist under consideration.

cation of Boyle's work. Torricelli had not yet seen the light of day, the pneumatic pump was unknown, and three hundred years must elapse before the work of Lavoisier and Priestley. However, on further examination of de Acosta's statement it becomes apparent that, although this astute observer practically indicated the fundamental cause of debility at low pressures, he failed to appreciate the correct significance of his observations for he states:

> And no doubt but the winde is the cause of this intemperature and strange alteration, or the aire that raignes there. For the best remedy (and all they finde) is to stoppe their noses, their eares, and their mouthes, as much as may be, and to cover themselves with cloathes, especially the stomacke, for the aire is subtle and piercing, going into the entrails, and not onely men feele this alteration, but also beasts, that sometimes stay there, so as there is no spurre can make them goe forward (1, p. 131).

Fifty years later Torricelli invented the barometer, and Otto von Guericke the pneumatic pump. These inventions were indispensable for the study of high altitudes, and provided not only the tools, but also the stimulus for a surge of work on this subject.

Robert Boyle has long been known as the "father of modern chemistry." Fulton is of the opinion one must include aviation medicine among his manifold progeny (17). Boyle's first scientific publication appeared in 1660 (7, 16). It is highly significant that a decompression chamber was instrumental in giving birth to the then revolutionary concept of respiration, significant because after almost 300 years of relative obscurity the decompression chamber, an instrument of physiological investigation is once again in prominence. (See Fig. 1).

Boyle demonstrated that air had "weight and spring." The latter notion seems to have captivated him, and it enters into many of his concepts. "Spring" is a highly descriptive word, since when air is compressed, it acts precisely as does a spring. He explained this phenomenon by drawing an analogy to a heap of wool, which after compression, regains its original volume. He had an alternative idea that the air consisted of particles which are in constant activity, and which collide, thereby repelling each other. Thus, when air is compressed, the chances of collision are greater, and the air, consequently, has a greater "spring."

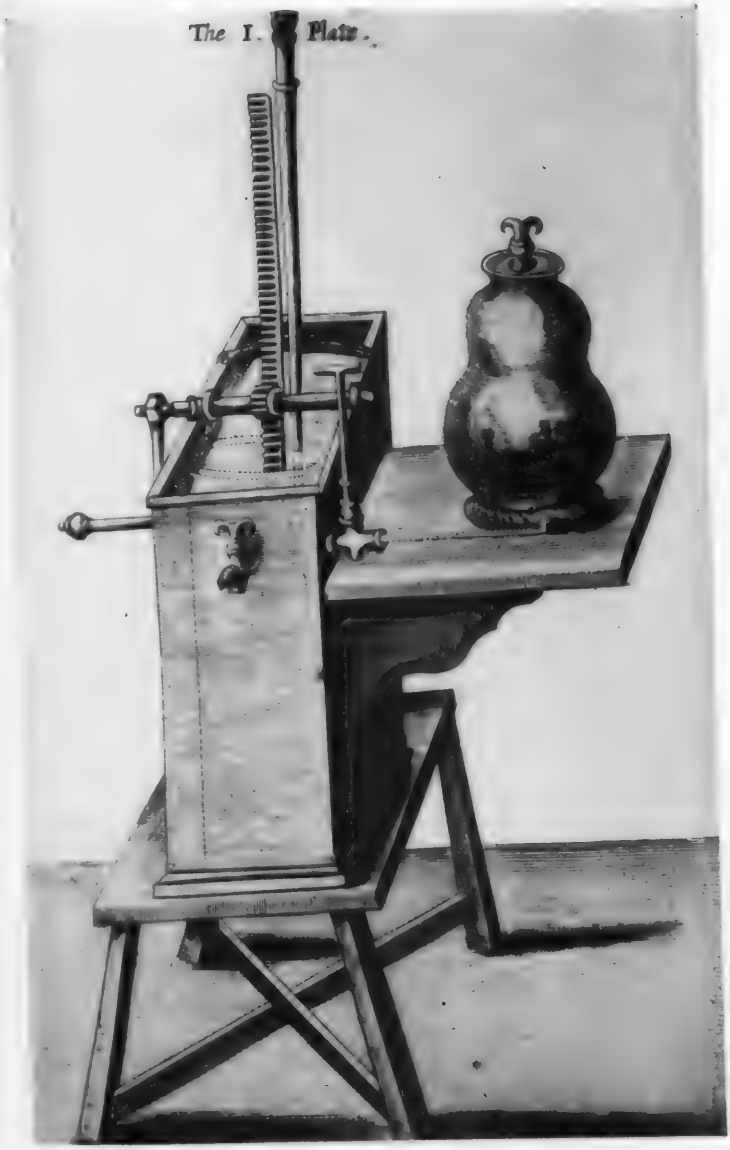

FIG. 1.

Decompression chamber of Robert Boyle, 1660.

These concepts laid the groundwork for his experiments on decompression. He was fortunate in having Robert Hooke as his technician, and the construction of the pumps used in these experiments is to be accredited to the latter. The following quotation demonstrates the exactitude and reserve exercised by Boyle in his experiments:

> All things being thus in readiness, the Sucker was drawn down; and, immediately upon the egress of a Cylinder of Air out of the Receiver; the Quick-silver in the Tube did, according to expectation, subside; and notice being carefully taken (by a mark fastened to the outside) of the place where it stopt, we caus'd him that manag'd the Pump to pump again, and mark'd how low the Quick-silver fell at the second exsuction. . . .
>
> Now (to satisfy ourselves further, that the falling of the Quick-silver in the Tube to a determinate height, proceeds from the *Aequilibrium*, wherein it is at that height with the external Air, the one gravitating, the other pressing with equal force upon the sujacent Mercury) we Returned the Key and let in some new Air; upon which the Mercury immediately began to ascend (or rather to be impell'd upwards) in the Tube . . . (7, p. 109).

On reading these lines one becomes encompassed by the tremendous tension of anxiety, and exaltation of satisfaction that must have gripped these men.

When a new field is unfolded for investigation the absolute extreme seems the most tempting, accordingly Boyle desired to create a perfect vacuum, and to see how an animal enclosed therein would react. His crude equipment frustrated this desire, and he had to satisfy himself with observations in partial vacuums. The experiments in which animals were subjected to various degrees of rarefaction are described in fascinating detail. He made the fundamental observation that a partial vacuum extinguished life concurrently with the extinction of a burning candle, a concept which paved the way for Hooke, Lower, Mayow, Priestley, Lavoisier, and Haldane to formulate our present day concept of respiration (15). He enclosed a wide variety of animals in containers of all sizes, and at varying pressures. The cause of death stimulated the imagination of many scientists of that day, and each suggested a novel hypothesis. Boyle considered several of them, and commented at some length on the following:

That it was not the want of Air that destroy'd them, but the Pressure of the innate Air in the cavity of the Chest; as if the Spring of this Air being no longer counterbalanc'd by the ambient Air, was thereby become so strong, that it kept the Thorax forcibly distended, and hinder'd its wonted contraction; and so compress'd the Lungs and their Vessels, as to obstruct the Circulation of the blood (*7*, p. 342).

Boyle gave this concept little credence since he observed augmented respiratory movement in his animals prior to death. Another conjecture stated,

That upon the sudden removal of the wonted pressure of the ambient Air, the warm blood of those Animals was brought to an Effervescence of Ebullition, or at least so vehemently expanded as to disturb the Circulation of the Blood and so disorder the whole Oeconomy of the Body (*7*, p. 345).

After carefully weighing every conceivable possibility, Boyle finally concludes:

. . . perhaps . . . there is some use of the Air which we do not yet so well understand, that makes it so continually needful to the Life of Animals. *Paracelsus* indeed tells us, That as the Stomack concocts Meat, and makes part of it useful to the Body, rejecting the other part, so the Lungs consume part of the Air, and proscribes the rest. So that according to our Hermetick Philosopher . . . we may suppose, that there is in the Air a little vital Quintessence . . . which serves to the refreshment and restauration of our vital Spirits, for which the grosser and incomparably greater part of the Air being unserviceable, it need not seem strange that an Animal stands in need of almost incessantly drawing in fresh Air. But though this opinion is . . . absur'd . . . it should not be barely asserted but explicated and prov'd (*7*, p. 362).

Professor Patterson has recently published an article on John Mayow, which contains several pertinent observations (34). Now that the correct interpretation of the problems that interested Boyle and the numerous other investigators before Bert has been made clear, one is tempted to read into the speculative conclusions of the former meanings that closer study will not substantiate. This point of view is magnificently expressed in the following quotation from Patterson,

That scientists from Paracelsus—and perhaps before Paracelsus—down to these discoverers dealt with and discussed phenomena that had indeed to do

with oxygen, is true, but it is greatly to force the meaning of the word 'discovery' to use it with regard to their investigations. Even when oxygen had been definitely and deliberately prepared by Priestley it took not only him, but also Lavoisier, the better part of a year, really to understand that something of an entirely unsuspected character had been obtained, and to impress upon scientists, actually for the first time, the presence of a second aeriform constituent in the atmosphere. There is no doubt that Bayen had made and collected oxygen before Priestley did, but he failed to recognize it as something new, and cannot therefore be regarded as having discovered it; and this applies with greater force to other unconscious preparations of oxygen by Hales and possibly by Robert Boyle, and, of course, still more strongly to the vague speculations of Hooke and Mayow (34, p. 539).

A salient observation in support of this thesis is the fact that Giovanni Francesco Cigna (9) was fully aware of the writings of Boyle, he repeated and extended many of the latter's experiments on decompression; yet he clearly had no concept of a vital constituent in the air. Cigna's work was published in 1761, a century after Boyle's first scientific book, but still 15 years before the discovery of oxygen. Boyle's discoveries led to an apparent contradiction, since animals died in his chambers at altitudes considerably lower than mountains upon which many persons travelled without experiencing any untoward effects. Cigna considered this point, and found that his animals would survive at decreased pressures if he periodically ventilated the chamber. He was led to this experiment by an ingenious preliminary observation, *i. e.* at the same reduced pressure an animal would live longer in a large chamber than in a small one. Thus, he reasoned that if the deleterious effect was to be attributed to the rarity of the air alone, the size of the chamber would make no difference. He then ventilated his chambers, and accordingly, found the explanation of survival on high mountains. He ultimately concluded from these experiments that the elasticity of the air is diminished by the noxious vapors, and finally when the air is saturated, it can take up no more, so that the animal is stifled. This conclusion is practically identical with the conclusions drawn by Boyle after his first experiments in 1660 concerning the function of respiration:

. . . to receive into it the superfluous Serositites, and other Recrements of the Blood, whose seasonable Expulsion is requisite to depurate the Mass of Blood (7, p. 351).

It is clear that Cigna did not take Boyle's suggestion to explain and prove the existence of "a little vital Quintessence."

There can be no doubt that the work of Boyle stands quite alone, both in depth of insight, and in time. The magnificent usage to which he had put the barometer of Torricelli, and the pump of von Guericke was neglected for many years, and in order to trace the growth of knowledge related to low atmospheric pressures, it is necessary to turn to the voluminous accounts of mountain expeditions and balloon ascents.

The philosophers and scientists of the 17th and 18th centuries were intrigued by the reports of travelers to high mountains, and without always utilizing the experimental method, and caution of interpretation, which characterized the work of Boyle, they formulated quite elaborate, but inadequate theories to explain the difficulties experienced in low atmospheric pressures. Borelli (5, see vol. 2, p. 242), Bouger (6), and many others explained the entire problem on a mechanical basis. Haller (20, see vol. 3, p. 191) made elaborate calculations, taking into consideration body surface to show the tremendous effect that a reduction in pressure should have on the body. These concepts remained paramount until after the discoveries of Priestley (35) and Lavoisier (25) in 1775.

De Saussure travelled extensively in the Alps, and in 1803 published eight volumes on his observation (38). The nausea experienced while at elevated sites stimulated him to formulate several explanations. It is quite apparent that he was unsure of his ideas, and attempted to incorporate every conceivable possibility. Interestingly enough, the following suggestion brought him close to the actual explanation:

> . . . que le ministère de cette fonction vitale n'étant pas complètement rempli, le sang, suivant la doctrine de M. Priestley, n'étant pas suffisament déchargé de son phlogistique, toute l'économie animale en est dérangée (38, vol. 2, p. 295).

Bouger had noticed many years before that man suffered from labored breathing at high altitudes, and he assumed that it was this effort which gave rise to mountain sickness. De Saussure pointed out that this could not be so, because prolonged and vigorous exer-

cise in itself did not give rise to any of the symptoms experienced at high altitudes. He finally generalized that it was the rarefied air which caused an immoderate acceleration of the respiration and circulation, and these factors, therefore must be the direct cause of the difficulties experienced.

Legallois (26) was interested in the relationship between the temperature of the blood and the quantity of oxygen absorbed. For these experiments he utilized a decompression chamber in an attempt to diminish the quantity of oxygen consumed, simultaneously observing the body temperature. There was a marked fall in the temperature of animals enclosed in the chamber, and he concluded, therefore, that the cold experienced by persons at high altitudes was due not only to the external environment, but also to the diminished quantity of oxygen respired.

The first person to attribute mountain sickness to low oxygen pressure was Clissold (10). In 1823, after a journey to Mont Blanc, he reported that the debility at these heights was due, in part, to the reduced quantity of oxygen in the atmosphere. As late as 1836 (33) it is remarkable to find the following view still being expressed:

> L'auteur a noté avec soin les circonstances observées sur lui et sur les guides qui l'accompagnaient. Elles sont si peu importantes qu'elles nous confirment dans l'opinion que la fatigue joue un plus grand rôle que la rareté de l'air ou l'influence présumée de la neige. . . . Nous pouvons affirmer que ce sont les mêmes sensations éprouvées par les voyageurs ordinaires quand ils approchent de la cime d'une montagne quelconque, après avoir monté pendant quelques heures (p. 151).

Again in 1841 (29) it is quite incredible to read:

> La vivacité de l'air, jointe à sa ténuité, ranime le voyageur et double ses forces car la composition chimique est la même (p. 213).

And again as late as 1843 Maissiat (27, see pp. 253-254) insisted that due to the reduction of pressure the abdominal gases would expand, and thereby give rise to the symptoms noted at these pressures.

During this period a few investigators interested in the etiology of mountain sickness attempted to associate the deficiency of oxygen in the atmosphere with this disorder, although by far the greater

number clung tenaciously to variations on the mechanical theme. In 1851 Payerne (36) attempted to prove that oxygen lack had nothing to do with the problem under discussion. Payerne was an engineer who merely carried out a simple calculation to prove his point. He demonstrated that at 22,000 feet the atmosphere would still contain 125 grams of oxygen per cubic meter. In an hour, a man with a ventilation of 800 liters would take in 100 grams of oxygen. Since at rest in that period of time, one converts only 50 grams of oxygen to carbon dioxide, it seemed to Peyerne that even allowing for increased exertion there should still be an adequate quantity of oxygen. This calculation weakened the oxygen theory considerably, and it was not until ten years later that Jourdanet pointed out the error (24). Jourdanet had the benefit of a recent experiment which demonstrated that the volume of oxygen in the blood cannot be accounted for on simple physical laws, but rather that a chemical affinity is established. On this fact he based his statement that since the oxygen pressure is reduced the volume of oxygen in the blood will be reduced regardless of the fact, as Payerne had pointed out, that there is, even at 32 cm. pressure actually enough oxygen in the atmosphere to satisfy metabolic needs.

In 1854 Conrad Meyer-Ahrens, a physician at Zurich (30) published a book dealing with this subject. He described the symptoms in great detail, and then attempted to determine the causes and their relative importance. He ascribed the major roles to the diminution of oxygen, the rapidity of evaporation, and the intensity of the reflection from the snow, while the direct effect of the reduced total pressure he considered only of secondary importance.

The diminution of oxygen appeared with increased frequency in the discussions of the primary cause of mountain sickness, but the mechanical explanation continued to appeal to many, especially the physicists. Even though in 1814 Valentin (4) stated:

> Nimmt man daher selbst für das mittelbare Volumen eines Menschen 4500 Cubikzoll an . . . , so würde dieser, wenn er selbst die gleiche Zusammendrückbarkeit wie das Wasser hätte, bei einem um 1 Atmosphäre verstärkten Drucke erst 0, 2 Cubikzoll oder 1/2252 des gesammten Körperumfanges verlieren. Man sieht hieraus, dass das Volumen eines Menschen, der sich auf dem Montblanc befände sobald derselbe in eine tiefe unter dem

Meeresspiegel liegende Höhle hinabstiege nur ungefähr um 7/100000 verlieren würde (vol. 1, p. 84),

Heusinger (21, see vol. 1, p. 252) in 1853 again attempted to explain the syndrome on this basis.

It will be recalled that Boyle considered and dismissed the concept dealing with the effervescence of blood at low pressures. Yet this phenomenon received consideration many times afterwards, and was directly observed in the experiments of Felix Hoppe (22), who quickly decompressed his animals, hurriedly autopsied them, and found bubbles of air in the blood. It is quite apparent that this phenomenon bears directly on the important subject of aero-embolism, but has no relation to the deleterious effects under consideration experienced at high altitudes, after an ascent at a more moderate rate. Hoppe, however, came close to performing the experiment which Bert did many years later, and which established the true relationship of oxygen to this problem. He desired to demonstrate that oxygen lack played no part in the phenomenon, and designed his experiment in such a way that he obtained results which seemed to demonstrate this point quite neatly. He placed an animal in his chamber, and rapidly withdrew the air, recording the pressure at which the animal collapsed. Then he repeated the experiment using oxygen instead of air, and found that the animal died at the same pressure; in view of this finding it is not surprising that he should conclude that oxygen lack was unimportant. It must be mentioned that his animals collapsed at a total pressure of 75 mm. Hg. Armstrong (2) has pointed out that at a pressure of 87 mm. Hg, due to the vapor and carbon dioxide pressures, an animal breathing pure oxygen will have little oxygen in its lungs. It is, therefore, not difficult to understand why Hoppe was deceived.

In this manner the controversy continued for the greater part of the 19th century. Mountain expeditions increased as did the height to which they ascended. From the vague generalized statements concerning the discomfort experienced at these altitudes, more precise and inclusive observations evolved. The aberrations of digestion, secretion, respiration, circulation, locomotion, and the nervous system were carefully noted, and attempts, sometimes cautious and rational, more often ranting and shallow, were made to explain

these symptoms. Only a few of the earlier theories have been discussed in detail, merely to give a background of the confused thinking characteristic of the period under consideration. These arguments, often in the exact form, or in an ill-concealed imitation, continued unabated until the work of Jourdanet, and the ill-fated flight of the "Zenith" (18, 39) inspired Paul Bert to carry out experiments, which in retrospect, it is difficult to understand how his predecessors failed to do.

In 1878 Bert (4) published a summary of this work. He reviewed previous investigations and concepts in meticulous detail. Before discussing his own theories he outlined the prevailing ones of the day. Many touched upon insufficient oxygenation, as we have seen, but none clearly developed this theme; others concerned themselves with elaborate, and even wondrous descriptions of the direct effect of diminished pressure in making respiration more difficult, in embarrassing the circulation, or in weakening the articulation; and the remainder had to do with the effusion of gases from the blood, or the dilation of gas in the intestines. Against such a varied and confused background, the direct accuracy and simplicity of Bert's experiments and conclusions stand out in poignant, yet brilliant, relief.

Bert carried out his experimental work in decompression chambers of varying sizes, and ultimately constructed one spacious enough to accommodate a man (Fig. 2).

Of the many conclusions drawn by Bert from his meticulous and laborious work, one stands out clearly as a momentous milepost along the circuitous, and obstructed road leading to the ultimate elucidation of this problem. By simply keeping the absolute pressure of oxygen constant, while lowering the total atmospheric pressure, he proved beyond cavil, that the symptoms above enumerated are due to the reduced oxygen pressure, and not to the diminished total pressure.

Paul Bert indicated that mountain sickness was primarily due to the diminished partial pressure of oxygen in the lungs. This conclusion has been challenged but three times; by Fraenkel and Geppert (14), by Longstaff (3, p. 2) and by Mosso (31).

In 1883 Fraenkel and Geppert criticized Bert's work on the

grounds that his analytical methods were not exact. They claimed that at least to a pressure of 41 cm. Hg (higher than Mont Blanc) the blood contains as much oxygen as it does at sea-level. It is perfectly true that at this pressure the steep descent of the oxy-

FIG. 2.

Decompression chamber constructed by Bert, 1878.

hemoglobin dissociation curve has not yet been reached, but it is now clear that even at 41 cm. Hg pressure there is a significant decrease in the oxygen saturation of the blood. Much confusion arose at that time because the investigators did not clearly differentiate

between oxygen content and oxygen saturation. Due to the process of acclimatization, which will be discussed presently, there may be a marked diminution in oxygen saturation at high altitudes, yet the oxygen content will be unaltered.

Longstaff concluded in 1906, from personal experience in scaling various lofty mountains, that the debility observed at elevated altitudes was due to a combination of " physical exertion, want of condition, and poverty of diet." He states that if the people who suffer from mountain sickness at the Peak of Teneriffe (12,200 feet), or Fujiyama (12,425 feet) were placed in a decompression chamber, and the pressure reduced to an equivalent extent they would suffer no ill effects. Barcroft (3) and his party avoided the conditions specified by Longstaff as being contributory to mountain sickness while climbing Teneriffe, yet they all, to varying degrees, exhibited the symptoms characteristic of this disease. Even more striking is the picture described by Douglas and his colleagues (11) of the tourists conveyed to the summit of Pike's Peak. Under these conditions the factor of fatigue was non-existent, yet the nausea experienced was marked. Barcroft also carried out experiments in a decompression chamber. He reported that at a simulated altitude of 18,000 feet he succumbed to mountain sickness. This is higher than the mountains above mentioned, but Barcroft had been in the chamber continually for six days during which time the pressure was gradually reduced. Under such conditions he had time to become acclimatized. Further, he did no work comparable to climbing a mountain, thus the discrepancy in the height at which the sensation of nausea appeared is hardly significant. It should be mentioned, however, that the factor of physical exertion listed by Longstaff as a primary cause of mountain sickness is an important consideration since oxygen want is actually the discrepancy between oxygen supply and oxygen demand. Accordingly, when the oxygen supply is reduced the degree of exertion will be a most important factor in determining the onset of the illness.

The argument advanced by Mosso was more challenging than the objections of Longstaff. Mosso's data was collected on a mountain expedition to Monte Rosa in the Alps, a few years after the publication of Bert's voluminous work. He repeatedly quotes the observa-

tions of Fraenkel and Geppert cited above, and also of Hufner (23) who carried out experiments on solutions of hemoglobin, and concluded that up to an altitude of about 30,000 feet the cause of mountain-sickness must not be sought in any physical or chemical change in the hemoglobin of the blood. Mosso apparently made no oxygen determinations himself, but came to the conclusion that reduced carbon dioxide pressure was the primary cause of mountain sickness, in the following manner:

> In Regina Margherita Hut I had with me Paul Bert's book on "Barometric Pressure," and on looking at the diagram showing the diminution of oxygen and carbon acid in arterial blood when the barometric pressure decreases, I saw at once that on high mountains there must be a greater lack of carbonic acid than oxygen in the blood (23, p. 287).

Mosso did a few experiments in a decompression chamber in which he varied the pressure of oxygen and carbon dioxide, and found that one could stand a greater reduction of oxygen if the pressure of carbon dioxide was simultaneously increased. He further showed that there was a decrease of carbon dioxide in the expired air at low atmospheric pressures. From these data he concluded that acapnia must be the cause of mountain sickness.

It is apparent that this conclusion is based upon grossly inadequate evidence. Mosso refrains from stating specifically why he thinks there should be a diminution of carbon dioxide in the blood, or in the alveolar air. He seems to have believed that the mere reduction of barometric pressure would of itself extract the carbonic acid from the body. It is axiomatic, as Barcroft points out, that:

> The body is exposed to what is practically a vacuum of CO_2, whether it be at the Capanna Margherita or in his own laboratory at Turin (3, p. 89).

Although the work of Mosso can be severely criticized in many respects, the role of carbon dioxide in the sequence of physiological changes which occur at high altitudes cannot be completely dismissed, in fact, most recent work on this subject indicates quite definitely that the loss of carbon dioxide from the blood due to hyperventilation is directly responsible for many of the alterations observed.

Barcroft made various determinations on himself, and on his colleagues which led him to believe that acapnia played no role whatso-

ever, and that reduced oxygen pressure, and increased hydrogen-ion concentration consequent to reduced oxygen supply were the fundamental factors in the production of this disorder. Subsequent investigations have established the fact, beyond any doubt, that the decreased partial pressure of oxygen is the primary link in the sequence of events which take place in the body when exposed to low atmospheric pressure, giving rise to mountain sickness, acclimatization, and perhaps ultimate deterioration.

After the turn of the century attention became focused upon the mechanism of acclimatization, for it was recognized that certain symptoms characteristic of first exposure to reduced pressure became mitigated, or even disappeared, upon prolonged exposure. Douglas, Haldane, Henderson and Schneider at Pike's Peak (11), Barcroft and his party at Teneriffe, and the several expeditions which attempted to reach the summits of Everest (8, 32, 37), all collected fundamental observations on the physiological mechanism of acclimatization.

The first effect of diminished oxygen pressure is increased ventilation. This is probably due to the action of reduced arterial oxygen pressure on the carotid body. The carbon dioxide content in the alveoli is, therefore, reduced which permits the existence of a greater partial pressure of oxygen. Thus, such a procedure would help to offset the effects of diminished oxygen in the atmosphere. It was observed, however, that the labored breathing characteristic of first exposure ultimately diminished. It was apparent that some bodily change had taken place which eradicated the necessity of increased ventilation. The Pike's Peak Expedition disclosed that prolonged exposure to low atmospheric pressure brought about an increase in hemoglobin. In fact, the increase of hemoglobin may be so great as to cause an actual increase in the oxygen content of the blood even though there is a fall in the percentage of oxygen as compared with total hemoglobin (12, 13). This accounts for the reluctance of many investigators to accept oxygen reduction as the primary cause of mountain sickness (23, 28, 31, 41). Fitzgerald (12, 13) points out that the symptoms of oxygen deficiency at high altitudes are, accordingly, due to deficiency, not in the amount, but in the partial pressure of oxygen in the arterial blood.

Haldane, Kellas and Kennaway (19), working with a decompression chamber extended the studies made by the Pike's Peak Expedition. Determinations on the blood and urine during exposure to low pressures, were made and the conclusion reached that the diminished oxygen pressure gives rise to over-ventilation, this in turn washes out the carbon dioxide thus producing an alkalosis, and the kidneys then take up the burden of eliminating base and bicarbonate, thereby, reducing the blood alkali. These investigators, however, insisted that the most important physiological adjustment of acclimatization was an increased inward secretion of oxygen by the lung epithelium, a theory advanced by Haldane and his co-workers at Pike's Peak. Barcroft stated that inaccurate analytical methods gave rise to this impression, and that actually the arterial oxygen pressure is always lower than the alveolar oxygen pressure, thus, he insisted, simple diffusion is adequate to explain the process, and that is the opinion held generally today.

It is quite understandable that attention should have been focused upon respiration, since labored breathing is the most obvious symptom experienced at high altitudes. The work briefly cited above is but a fraction of the observations recorded concerning the changes that take place in respiration and circulation. Investigations were ultimately extended to include kidney function, but the various other organ systems were neglected. This is most certainly not due to the lack of insight on the part of the investigators, but rather to the paucity of knowledge concerning the function of certain systems at that time. Barcroft was vividly cognizant of the fact that many problems remained to be elucidated since he ends his book by quoting a doctrine which he says,

> " has come through the ages. If one member suffers all the members suffer with it . . . the whole body fitly joined together and compacted by that which every joint supplieth according to the effectual working in the measure of every part maketh increase of the body to the edifying of itself " (3, p. 178).

The work of Boyle, Bert, Douglas, Haldane, Henderson, Haggard, Schneider, Barcroft, Sundstroem, and their collaborators, as well as many others, has established the broad general outline of the sequence of physiological changes that the body undergoes in an atmosphere of

reduced pressure. Under the compelling stimulus of the present world conflict, which includes fighting under anoxic conditions, the attention of investigators overywhere has once again been sharply focused upon these elusive problems.

Summary

Our knowledge of the physiology of anoxia began with the work of Robert Boyle in the 17th century. He made the fundamental observation that life could not be sustained at reduced atmospheric pressures. Since the investigation was carried out many years before the preparation of oxygen was achieved, it is not surprising that Boyle was unable correctly to explain his findings. During the next two centuries the problem of mountain sickness held the attention of many scientists. A few of the many and varied concepts to explain the debility suffered by persons at high altitude, touched upon diminished pressure of oxygen as the prime etiological factor, but it remained for Paul Bert, in 1878, to offer irrefutable proof. During the past forty years physiological alterations in the respiratory and circulatory systems of an organism exposed to low atmospheric pressure have been determined. Recently, it has become evident that other organ systems also play a role in the process of adaptation, and once again the physiology of anoxia is of current interest.*

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THE AFTERMATH OF CHARLES BELL'S FAMOUS "IDEA"

J. M. D. OLMSTED

Anyone who comes upon a modern reference to the discovery of the functions of the spinal nerve roots [1] is almost certain to gain the impression that Charles Bell's pamphlet, "Idea of a New Anatomy of the Brain," privately printed in 1811, was written with the sole purpose of showing that the dorsal roots are sensory and the ventral roots motor. Strangely enough the pamphlet not only fails to make this distinction of function for the spinal nerve roots or even to imply it, but Bell had no such object in mind when he wrote. The subject of the spinal nerve roots was introduced only as a part of the proof of his main thesis, which was the general principle that different parts of the nervous system, particularly the cerebrum and cerebellum, have different functions. It is the story of the final disproof of the evidence which Bell brought forward to support his thesis which concerns us here.

In Bell's own words he was attempting in the "Idea" to combat the "prevailing doctrine of the anatomical schools . . . that the whole brain is a common sensorium . . . and that the mind by the same nerves which receive sensation, sends out the mandate of the will to the moving parts of the body" (p. 4); [2] and to prove "that the cerebrum and cerebellum are different in function as in form; that parts of the cerebrum have different function; and that the nerves which we trace in the body are not single nerves possessing various powers, but bundles of different nerves whose filaments are united for the convenience of distribution, but which are distinct in office, as they are in origin in the brain" (p. 5). . . . "That the

[1] See for example Max Neuburger's *British Medicine and the Vienna School*, Wm. Heinemann, London, 1943.

[2] Since only three copies of this pamphlet are known to be in existence, and since the accuracy of reprintings is often not to be relied upon, the passages quoted, although they were taken from the 13th volume of Karl Sudhoff's *Klassiker der Medizin*, have been verified by me by comparing them with the copy of the original edition in the British Museum, which bears on a flyleaf in ink the inscription, "With Mr. Bell's respectful compliments, 34 Soho Square."

nerves of sense, the nerves of motion, and the vital nerves are distinct through their whole course, though they seem sometimes united in one bundle; and that they depend for their attributes on the organs of the brain to which they are severally attached" (p. 6).

This last sentence is of the utmost importance for an understanding of Bell's "Idea." Here he gives his classification of nerves into three categories, sensory, motor and vital, and the object of his whole argument is to show which parts of the brain preside over the three functions, sensation, motion and vital properties. The first two functions are perfectly clear, but we must look to Bell himself for a definition of "vital nerves." He says (p. 15): "The secret operations of the vital organs suffer the control of the brain, though we are unconscious of the thousand delicate operations which are every instant going on in the body." It is evident that by this he meant what we might now term the autonomic nervous control of the viscera and other organs.

In Bell's opinion (p. 21) it was difficult if not impossible to experiment directly on the brain itself. Since, he said, "we can trace down the crura of the *cerebrum* into the anterior fasciculus of the spinal marrow, and the cruca of the *cerebellum* into the posterior fasciculus," he thought he could "touch" the cerebrum by stimulation of the anterior fasciculus of the cord, and the cerebellum by stimulation of the posterior fasciculus. He "found that injury done to the anterior portion of the spinal marrow, convulsed the animal more certainly than injury to the posterior portion" (p. 21). Then follow the now famous two short paragraphs which are always quoted by themselves divorced from their context, and entirely misinterpreted.

"Next considering that the spinal nerves have a double root, and being of the opinion that the properties of the nerves are derived from their connections with the parts of the brain, I thought I had an opportnuity of putting my opinion to the test of experiment, and of proving at the same time that nerves of different endowments were in the same cord, and held together by the same sheath.

"On laying bare the roots of the spinal nerves, I found that I could cut across the posterior fasciculus of nerves, which took its origin from the posterior portion of the spinal marrow without convulsing the muscles of the back; but that on touching the anterior

fasciculus with the point of the knife, the muscles of the back were immediately convulsed" (p. 22).

This experiment led him to conclude that "the cerebrum and cerebellum were parts distinct in function. . . . The spinal nerves being double, and having their roots in the spinal marrow of which a portion comes from the cerebrum and a portion from the cerebellum, they convey the attributes of both grand divisions of the brain to every part" (p. 23).

Now what did he think were the attributes of these two grand divisions of the brain which were conveyed along the different columns of the spinal cord and the spinal nerve roots? Into the cerebrum he said "all the nerves from the external organs of the senses enter; and from it all the nerves which are agents of the will pass out" (p. 27). The cerebrum was, therefore, the seat of both sensation and motion; the ventral columns of the spinal cord and the ventral roots of the spinal nerves were both sensory and motor; and the proof was that stimulation of the ventral roots caused observable convulsion of the limbs. Of the cerebellum he says (p. 36): "The secret operations of the bodily frame, and the connections which unite the parts of the body into a system, are through the cerebellum and the nerves proceeding from it." The key word is "secret" as is shown by its being used not once but three times (pp. 15, 25, 36) when "vital" nerves are mentioned. The proof of these "secret operations" lay in his finding that nothing visible happened when he stimulated the posterior roots.

The anatomy and physiology expressed in his "Idea" can be summed up thus: the cerebrum is the center for both sensation and motion, the pathway for both these functions is over the ventral columns of the spinal cord and the ventral roots of the spinal nerves; the cerebellum is the center for unconscious impressions from the body itself and involuntary movements, and their pathway is over the dorsal columns of the spinal cord and the dorsal roots of the spinal nerves.

That Bell ascribed both sensory and motor functions to the ventral roots is universally ignored, but this fact was very early pointed out by Johannes Müller. In a footnote of the English translation (1844) of his famous *Elements of Phsiology* are to be found these words:

" He (Bell) seems, it is true, to have supposed at first that the anterior roots contained nervous fibers for sensation as well as those for motion, while the posterior roots governed the ' operations of the viscera ' " (p. 304). Augustus Waller [8] in his acrimonious debate with Sir Arthur Keith made the same point over and over again but apparently without impressing his opponent. Bell's guess as to the specific functions of the dorsal and ventral roots was no nearer the truth than that of Alexander Walker, who seems to have been the first actually to propose that one set of spinal nerve roots serves for sensation, the other for motion. Walker's suggestion was published in the *Archives of Universal Science* in July, 1809, two years before the printing of Bell's pamphlet, but Walker ascribed sensation to the ventral roots and motion to the dorsal roots. It is interesting to note that Walker had the same conception of the relation of the dorsal and ventral columns of the cord to the dorsal and ventral nerve roots as Bell had, but to be consistent Walker had to say that sensory impressions were conveyed in an " ascending " direction via the ventral columns of the cord, while the dorsal or " descending " columns presided over motion.

Bell's thesis that different parts of the brain and individual nerve fibers have their own functions was an excellent one and is held to this day. He should be credited with having stated what is usually known as Johannes Müller's Law of Specific Nerve Energies. It is true that this concept had been foreshadowed by previous writers. For example, Bichat, who died in 1802, said in his lectures on General Anatomy, " Each nerve fiber, though belonging in its course to many nerve trunks, can very well fulfill its function in an isolated manner." But no one had attempted to locate the precise divisions of the central nervous system which serve as centers for motion, sensation, and those obscure nervous actions which maintain the life of the individual, in just the way Bell attempted to do, viz. by stimulation of remote parts supposedly connected with these centers. It will be seen that the basis for Bell's deductions was the possibility of his tracing true anatomical connections between the parts in question, and the soundness of his conclusions depended on the accuracy

[8] See *The Lancet*, vol. 80, pp. 470, 614, 835, 967, 1032, 1718. Also *Science Progress*, 6: 78, 1911.

with which he could establish such relations. It was unfortunate that the anatomical methods of that era could not give a true picture of the relationship of nerve pathways within the central nervous system.

When Magendie [4] in 1822 began his series of experiments which demonstrated that the dorsal roots were, as he expressed it, "mainly for sensation," and the ventral roots "mainly for motion," this was entirely new light on the question, and Bell at once revised his earlier conjecture. He now considered the dorsal roots to be purely sensory, and because of their supposed connections with the cerebellum via the dorsal columns of the spinal cord, the cerebellum must be the seat of sensation; the ventral roots to him now became purely motor, and since they were connected with the cerebrum via the ventral columns, the cerebrum became the center for motion. The vague "secret" nervous processes formerly attributed to the posterior columns and posterior roots were played down, but he added a respiratory function to the lateral columns of the spinal cord whose seat was in the medulla.

Since only 100 copies of the 1811 pamphlet had been printed and distribution had been made only to the author's private friends, this work was unknown to the scientific world. In 1824 Bell republished certain of his papers previously read before the Royal Society under the title, "An Exposition of the Natural System of the Nerves of the Human Body" prefacing them with a short introductory essay in which he outlined his revised concept as to the location of the different nerve centers. The book had immediate and wide recognition. It was immediately reprinted in the United States, and translated into French. It is to this book and particularly its subsequent editions which bore the title of "The Nervous System of the Human Body" (1833 and 1844) that most commentators have been forced to go for information regarding the famous "Idea." For example, Sherrington in his section on the spinal cord in Schäfer's well-known *Text-book of Physiology* says in a footnote (v. II, p. 279): "An Idea of a New Anatomy of the Brain, 1811, republished in 'An Exposition of the Natural System of the Nerves,' London, 1824." This is, of course, absolutely incorrect. It is true that the main

[4] *Journ. de Physiol. expér. et path.*, **2**: 276, 1822.

theme of the " Idea " is outlined in the first few pages of this edition of the book, but because of the changes just noted, an utterly different impression from the original " Idea " is conveyed, and there is nothing to indicate that there was any change in attitude on Bell's part between 1811 and 1824. The later editions did contain excerpts from the " Idea," but only those passages were quoted which were consistent with an interpretation favoring the implication that the ventral roots were for motion and the dorsal roots for sensation.

One of the clearest statements of Bell's position at this juncture is to be found in certain passages of the 6th edition of his "Anatomy and Physiology of the Human Body " published in 1826, which were repeated verbatim in the 7th edition in 1829. He says (p. 24): " I imagine that the same column or tract which gives origin to the fourth, seventh, glossopharyngeal, par vagum, and spinal accessory nerves, is continued downward along the lateral part of the spinal marrow, and that it affords roots to the spinal nerves, constituting them respiratory nerves, as well as nerves of motion and sensation." And on p. 29, " We have already explained that the cerebrum has connection with the anterior columns of the spinal marrow, and the cerebellum with the posterior columns. And no one has given reason to doubt the correctness of the statement I have made that the anterior column is for motion, and the posterior for sensibility. If we were to indulge in opinions which we could not bring to the test of experiment, we should say that the cerebrum had power over the motions of the body, and the cerebellum over its sensibility."

By 1844 Bell again changed his opinion, and returned to his former position that the cerebrum is the center of both sensation and motion. But he now claimed that he could " trace with equal precision " the dorsal columns of the cord into the pyramids at the base of the medulla, and eventually to the cerebrum (p. 22 of the 3rd edition of " The Nervous System "). Thus he still retained the fundamental aspects of his scheme as regards the relation of the three columns of the cord to the spinal nerve roots, and the extension of the functions of sensitivity, motility and respiration from centers in the nervous system out to the spinal nerve roots via these columns.

The division of each half of the white matter of the spinal cord into three columns—a dorsal column extending from the dorsal or

median fissure to the exit of the dorsal roots of the spinal nerves; a lateral column lying between the two sets of roots; and a ventral column lying between the exit of the ventral roots and the ventral median fissure—had come down from the time of Haller and Chaussier in the 18th century. After Magendie's experiments of 1822 had shown that operations on the spinal cord in living animals were a possibility, a great number of investigators tried their hands at cutting these columns separately at different levels. Rolando[5] came to the conclusion that section of the dorsal columns abolished movement but left sensibility. Ludwig Türk [6] thought he had proved that the lateral columns were the sole conductors of sensitivity. Others held still other views.[7] Bell's concepts prevailed, however, until 1855. In England it was his brothers-in-law, the Shaws, who championed his cause. In France he had a particularly vociferous advocate in F. A. Longet whose reputation was very high in the 1840's. In a separate pamphlet (1841)[8] as well as in his extensive *Treatise on Physiology* (1850) he aired the whole Bell-Magendie controversy in a light unfavorable to Magendie. In fact, his whole life seems to have been motivated by an insatiable desire to point out Magendie's mistakes. Longet added his own confirmation of what had now come to be called "Bell's doctrine" or even "Bell's Theorem." When he transsected the spinal cord he found that stimulation of the dorsal column generally produced no movement; stimulation of the lateral and ventral columns produced no pain; the cephalic portions of the dorsal columns were exquisitely sensitive; the caudal portion of the ventral columns readily caused motion; and stimulation of the gray matter produced neither movement nor pain.

By this time Bell's assumption of a respiratory function for the

[5] *Sperimenti sui fascicoli del midollo spinale,* Torino, 1828.

[6] *Sitzungberichte der Math. Naturwiss. Classe de K. Akad. d. Wissensch. zu Wien,* April, 1851.

[7] See page 54 of Brown-Séquard's *Soc. Biol.* memoir of 1855 for a complete list of discordant views regarding the pathway of transmission of sensory impulses to the "common sensorium," and of motor impulses to the muscles.

[8] *Recherches expérimentales et pathologiques sur les propriétés et les fonctions des faisceaux de la moelle épinière et des racines des nerfs rachidiens précédées d'un examen historique et critique des expériences faites sur ces organes depuis Sir Ch. Bell, et suivies d'autres recherches sur diverses parties du système nerveux,* Paris, 1841.

lateral columns had been dropped and Rolando's contention that each lateral half of the spinal cord should be considered to consist of two columns, "posterior" and "antero-lateral" had been widely adopted. Longet's confirmation of Bell's doctrine therefore related only to the functions of these two columns of the spinal cord and the corresponding spinal nerve roots. Longet said of Bell's doctrine that it was "one of the most beautiful, the most fecund and withal the *best established*, as we claim to have shown elsewhere, even to the most critical of minds" (p. 37 of his 1841 pamphlet).

In spite of the supposed unassailability of Bell's doctrine, especially after it had attained the refined form which Longet had given it, a dissenting voice was presently heard, but because of its source it caused no alarm.

On January 3, 1846, a 28-year old medical student defended before a committee of the Paris Faculty of Medicine for his M. D. degree a thesis entitled, "Researches and Experiments on the Physiology of the Nervous System." The author had been born in Mauritius while that island was in the possession of England, the son of a Philadelphia captain in the U. S. Merchant Marine and his wife, a lady of French descent. The thesis is signed simply C. E. Brown, but as the young man shortly added his mother's patronymic to his own, in order, he said, to distinguish him from the other Browns, he was none other than Charles Édouard Brown-Séquard. Half of his thesis was a criticism of Marshall Hall, and half a criticism of Longet. In the latter half we find the following remarkable statements: "I cut the posterior columns . . . sensitivity remained without great diminution in the parts lying behind the section." Again, "after having cut the antero-lateral and the posterior columns on one side of the cord in frogs, pigeons and rabbits, I have found the parts situated behind the section and on the same side to be apparently as sensitive as those on the sound side." There was not the slightest ripple of excitement over these unorthodox statements, for who pays attention to a student's thesis? The young man was undiscouraged and moreover, he was persistent. He reported his findings to the Paris Academy of Science in 1847, and when the Société de Biologie was founded in 1848 he not only made similar reports before its members, but he performed the operation of hemisecting the cord

FACULTÉ DE MÉDECINE DE PARIS.

THÈSE

POUR

LE DOCTORAT EN MÉDECINE,

Présentée et soutenue le 3 *janvier* 1846,

Par CHARLES-ÉDOUARD BROWN,

né au Port-Louis, île Maurice (île de France),

DOCTEUR EN MÉDECINE.

RECHERCHES ET EXPÉRIENCES

SUR LA

PHYSIOLOGIE DE LA MOELLE ÉPINIÈRE.

Le Candidat répondra aux questions qui lui seront faites sur les diverses parties de l'enseignement médical.

PARIS.

RIGNOUX, IMPRIMEUR DE LA FACULTÉ DE MÉDECINE,
rue Monsieur-le-Prince, 29 *bis*.

1846

1846. — *Brous*.

of a guinea pig during the meeting of December 1, 1849. He cut the right half of the cord and showed that sensitivity persisted on the right side of the animal below the cut, and how was this possible if sensation was conveyed to the cerebrum via the dorsal columns of the cord? Nevertheless an autopsy performed by Claude Bernard verified the site and extent of the lesion. Even this brought no recognition that Brown-Séquard had made a fundamental discovery which was eventually to overthrow the major point of Bell's doctrine.

During the next three years Brown-Séquard reported experiment after experiment to the Paris Société de Biologie showing that transmission of sensation in the cord involves a crossing from one side to the other, and, what was still more incredible, far from the animal's losing sensitivity on the same side of the body below the site of hemisection, the parts bordering on the lesion were generally hypersensitive as compared with other parts. In 1852, fearing that his republican leanings were getting him into trouble with the French Government, he left hastily for the United States. Here he did more experiments and published two books on the subject. After a trip to his birthplace, Mauritius, to serve during the cholera epidemic, and a return to the United States where he accepted the professorship of physiology at the Medical College of Virginia at Richmond, we find him in 1855 back before the Société de Biologie in Paris still hammering away at his old thesis.[9]

At the session of the Society held on June 23, 1855, he sectioned the dorsal columns of the spinal cord in two rabbits, and again showed that sensitivity was not interrupted but that it was even increased in the region immediately below the lesion. Bell's doctrine died hard and even yet there were skeptics. It was said that the rabbit's cord was too small for one to be sure that the dorsal columns were completely severed and that larger animals should be used. A committee headed by Paul Broca, who, although seven years Brown-Séquard's junior, had made so meteoric a rise in the medical profession that he was already agregé in the Paris Faculty of Medicine and surgeon at the hospitals, was appointed to view Brown-Séquard's

[9] Recherches sur la voie de transmission des impressions sensitives dans la mœlle épinière (mémoire communiqué à la Société de Biologie en mai, juin et juillet 1855) *Mém. Soc. Biol.* 2, Ser. 2, 51, 1855.

attempt to hemisect the spinal cord of a horse and a sheep at the veterinary school at Alfort. (Apparently elephants were too difficult to come by for experimental purposes.) The other members of the committee were Claude Bernard, Vulpian and two professors from the veterinary school itself. The operations were successful as well as further demonstrations which Brown-Séquard performed on rabbits, guinea pigs and dogs. The committee was absolutely convinced of the correctness of Brown-Séquard's point of view as to the crossing of sensory fibers in the cord and of hypersensitivity below the section.

It was Broca's report [10] of this committee read before the Paris Société de Biologie July 21, 1855, which finally gave the necessary push that " overthrew the edifice so securely cemented together, whose foundations had been laid by Charles Bell, and whose capstone had been sealed in place by Longet " (Broca's Report, p. 27). The symptoms appearing after hemisection of the spinal cord, which are, in broad outline, disappearance of sensation on the opposite side of the body below the lesion and motor paralysis on the same side, are now called the " Brown-Séquard Syndrome," and are well known to all physiologists and physicians. Only after the introduction of Waller's method of tracing nervous tracts by degeneration and the Marchi method of staining, did our knowledge of pathways in the central nervous system become precise. The anatomical methods of Bell's day were too crude to give this information, but so great was his authority that for more than a quarter of a century the incorrect evidence he had adduced to support his famous " Idea " was the accepted neurological doctrine whose validity it was heresy to question.

[10] Rapport sur les expériences de M. Brown-Séquard relatives aux propriétés et aux fonctions de la mœlle épinière, lu à la Société de Biologie, le 21 juillet 1855. Paul Broca, *Mém. Soc. Biol.*, 2, Ser. 2, 23, 1855.

HOW A PHYSIOLOGIST ANTICIPATED A PHYSICAL CHEMIST

N. S. RUSTUM MALUF

We fully recognize that Physiology, which uses the tools of Physics and Chemistry, advances in the wake of progress made by the basic sciences. The reverse, however, has sometimes occurred. Perhaps the best known instance of a discovery in Physiology stimulating one in the fundamental sciences is that which led to the invention of the voltaic pile. The physiologist and physician, Luigi Galvani (1737-98), suspended the hind-legs of a frog by a copper-hook from an iron-ballustrade; whenever the preparation touched the ballustrade the muscles contracted (1791). Galvani attributed the spasms to the conductance of animal electricity by metals. The physicist, Alessandro Volta (1745-1827), denied Galvani's conclusion and correctly stated that the contraction resulted from electricity generated by contact of two dissimilar metals. The polemic which followed stimulated Volta to invent the voltaic pile (1800). The discovery of oxygen and of carbon dioxide by the chemist and physiologist, Antoine Laurent Lavoisier (1743-94) had been conceived by several physiologists (cf. Patterson, 1931; Fulton, 1935) and Joseph Priestley (1733-1804), clergyman, chemist, and physiologist, and by the physician and chemist, Joseph Black (1728-99) respectively. Here, too, Physiology played a prominent rôle.

In this paper we wish to describe how a physiologist antedated a physical chemist by being the first to categorize, implicitly but distinctly, substances according to whether they can diffuse through organic membranes.

In 1861, the Scottish physical chemist, Thomas Graham (1805-69), son of a merchant and manufacturer of Glasgow, while master of the Mint, separated solutes into "colloids" and "crystalloids." The colloid was defined by inability to crystallise, low diffusibility, formation of gelatinous hydrates, being held in solution by very feeble forces, chemical inertness, physical aggregation, capacity of being a medium for the diffusion of liquids, cementation (of some)

at high temperature, mutability, ability to separate out water [syneresis], and inability to dialyse. He wrote that

as gelatine appears to be of this type, it is proposed to designate substances of the class as *colloids*, and to speak of their peculiar form of aggregation as the *colloidal condition of matter*. Opposed to the colloidal is the crystalline condition. . . . It may perhaps be allowed to me to apply the convenient term *dialysis* to the method of separation by diffusion of gelatinous matter. The most suitable of all substances for the dialytic septum appears to be the commercial material known as vegetable parchment or parchment-paper, which was first produced by M. Gaine, and is now successfully manufactured by Messrs. De la Rue . . .

The physiologist, Carl Friedrich Wilhelm Ludwig (1816-95), confirmed (1844) the anatomical observations of William Bowman (1816-92) on the renal unit and its blood-supply (1842) and gave his first theory of how the renal unit functions. Only the part which concerns us, namely, that regarding glomerular function, will be quoted:

. . . after hydraulic laws, a significant pressure would be exerted on the walls of the vessels by the current of blood which, here, flows from a narrow lumen (the afferent vessel of the glomerulus) into a broad one (the glomerulus itself) and then again into a narrow one (the efferent vessel). By this pressure, a certain quantity of liquid would have to be pressed out through the fine walls of the vessels. This part of our view can indeed hardly be called hypothesis. We now assume further, hypothetically however, that these vessel-walls possess characteristics which permit, of the fluid and dissolved substances of the blood, passage through them only of water, a part of the extractible materials, and the free exclusively water-soluble salts; while the entire protein-materials, the fats, and the existing mineral constituents bound to both are withheld from passing. This, at first glance, somewhat ventured hypothesis loses much of its apparent exaggeration if one will recall the most interesting research of Brücke regarding endosmotic currents and according to which the membrane of the egg-shell is impermeable to proteins, and the remarkable investigations of Matteucci and Cima on endosmosis through animal-skins. Now, on giving room to this viewpoint, one would have, in the beginning of the tubules, a fluid which would actually possess all constituents of the urine and perhaps, also, all solid constituents in identical relative amounts with regard to one another as in the urine but in much more water than in the latter.

Both Marcello Malpighi (1628-94) and Bowman believed that, volumetrically at least, most if not all of the urine is separated, from

the blood, in the renal corpuscle. How this separation occurs, Malpighi (1666) *could* not and Bowman (1842) *did* not conceive. There is a vague hint in Bowman's discussion that the process might be by filtration and he certainly does not state that it is by secretion. Hence it is incorrect to identify Bowman's theory of renal function with that of Heidenhain (cf. Maluf, 1942).

If Bowman were equipped with the physico-chemical knowledge of Ludwig he certainly would have given a theory of glomerular function identical with that of Ludwig. The latter had made one of his aims to explain " vital " phenomena in the terms of Physics and Chemistry. When, in 1847, he visited Johannes Müller's laboratory in Berlin, he there met three men: Hermann Ludwig Ferdinand von Helmholtz (1821-94), Emil Heinrich du Bois-Reymond (1816-96), and Ernst Wilhelm Brücke (1819-92). These men, of nearly identical ages, formed a concurrent quadrumvirate which became the main base and source of subsequent physiological inquiry. Ludwig stated

> We four imagined that we should constitute Physiology on a chemico-physical foundation, and give it equal scientific rank with Physics, but the task turned out to be much more difficult than we anticipated (Sanderson, 1896).

Ludwig's theory of glomerular function, quoted above, assumes that (1) a liquid can be driven through membranes (the glomerular membrane, specifically) by pressure; that (2) the membranes are differentially permeable; that (3), of the solutes of the plasm, the membranes are impermeable only to the proteins, the fats, and any minerals that may be bound to the proteins and to the fats, i. e., the membranes are impermeable only to " colloids," to use Graham's (1861) word prematurely; and that (4) minerals can be bound by proteins. The existence of " colloids " versus " crystalloids " and of " dialysis " was clearly implied although no technical names were given.

In analysing the sources from which Ludwig must have, implicitly, derived his theory, we shall see that he lived up to his word by familiarizing himself with the latest discoveries in the fundamental sciences. The contributions from which Ludwig doubtless bor-

rowed will be described under the headings given in the preceding paragraph:—

1. A liquid can be driven through a membrane by pressure.— Philippe de la Hire (1640-1718), French astronomer, architect, physicist and mathematician, son of the painter Laurent de la Hire (1606-56), was elected member of the Académie des Sciences, Paris, in 1678, and subsequently became professor at the Collège de France and at the Academy of Architecture. He was the father of two distinguished scientists: Gabriel-Philippe de la Hire (1677-1719), an astronomer and physicist, and Jean-Nicolas de la Hire (1685-1727), a botanist. Philippe turned the "fresh" bladder of a pig inside out and then filled it with water to the extent of three-fifths of its extensible capacity. The water issued at various points and within 12 hours nearly half of it had seeped out. He assumed that, in the normal state, that is, when not turned inside out, water (or urine) does not ooze through the bladder and thus conjectured that valves protect the numerous fine pores.

In 1714, the celebrated French physicist and zoologist (both experimental and descriptive), René-Antoine Ferchault de Réaumur (1683-1757), instead of creating a supra-atmospheric pressure upon the water, as la Hire had done, caused the seepage of water through a membrane by producing a subatmospheric pressure on the side opposite to that of the water:

> It nevertheless occurred to me several times, and indeed very frequently, to close the extremity of a tube with pig-bladder in such a way that air cannot penetrate it. This gave me the occasion to try out an experiment which appeared to me capable of showing whether there are bodies through which water traverses but through which air cannot traverse. . . . For this I closed the end of a tube with the bladder. . . . I constructed a rim around this end of the tube with my mixture of wax and pitch, thus forming a little cup with the bladder as the bottom. I filled the tube with mercury and reversed it; the mercury stayed at about 18 inches [*Torricelli's experiment, 1643; the thumb was put over the open end of the mercury-filled tube as that end was tipped into a container of mercury*]. I noted, by comparing this tube to a barometer or to a thermometer, that the mercury remained stable so that I was sure that the external air had no communication with the mercury of the tube. I then filled the little cup, which I had made at the end of the tube, with water. The water penetrated the bladder and fell on the

mercury although quite slowly. . . . From this it follows that air plus water can, under certain circumstances, pass through routes which air [*alone*] cannot pass.

2. Organic membranes are differentially permeable. The discovery that some membranes will permit passage of water to the relative exclusion of various solutes was inseparably connected, from the very beginning, with observations on osmosis. Because knowledge of differentially permeable membranes advanced in unity with studies on osmosis it will be necessary to discuss the former by means of the latter.

Osmosis and the differential permeability of membranes was first discovered by the French abbot and physicist, Jean-Antoine Nollet (1700-70). The discovery was admittedly an accidental by-product of experiments carried out to find the causes of ebullition (1748). The work is classical and deserves quotation:

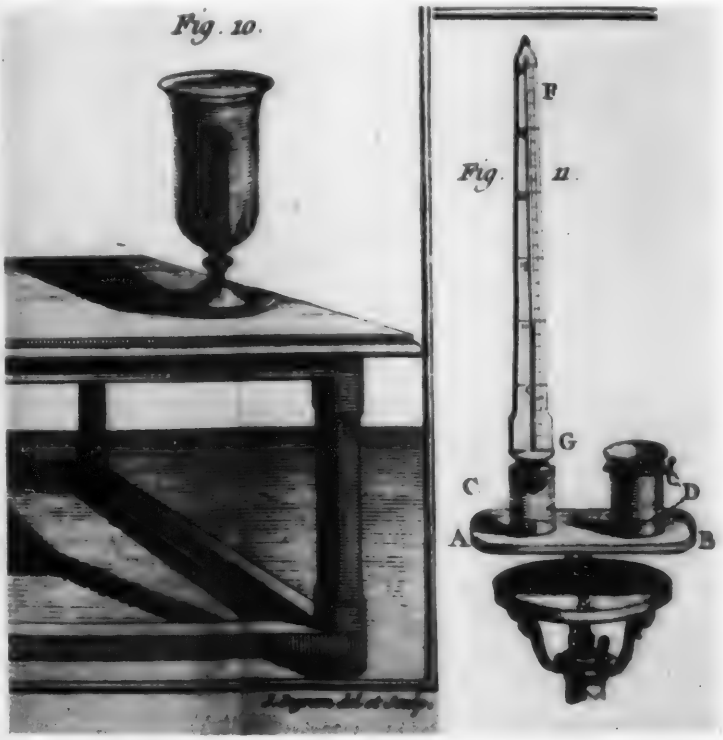
> Before finishing this memoir, I think it necessary to give account of a phenomena which I struck by chance and which, at first glance, appeared as singular as that of the mercury depressed below its level.
>
> I had put some spirit-of-wine in a spacious container; I had purged it of air [*by a pneumatic pump*]; and I had exhausted its ebullition; I had wanted to find if, without absorbing any new air, it could boil again after an interval of several days: for this purpose I had filled [*with spirit-of-wine*] a cylindrical vial of five inches in length and one inch in diameter; and having covered it with a piece of moistened bladder, which was tied to the neck of the vial, I plunged it into a large container filled with water after having ascertained that no air entered into the spirit-of-wine (see fig. 10). I was much surprised, after five or six hours, to find that the vial was more full than at the time of its immersion. . . . The bladder, which served as a stopper, became convex and so taut that, on pricking it with a needle, a jet of liquid issued which rose over a foot in height.

The temperature of the liquids in the inner and outer vessels was found to be identical; hence it was established that changes in temperature could not have been the cause. Converse results were obtained by putting water inside the vial and wine outside.

When the vial was only half-filled with spirit-of-wine, covered with a bladder, and immersed as above, no water entered into the vial and the quantity of liquid in it remained the same; when the container was reversed, water entered.

It is quite clear that immediately the spirit-of-wine touches the bladder, it forms with it a body through which water penetrates apparently by the same force that makes it enter rapidly into sponges. . . .

Upon consideration I think that the bladder may indeed be more permeable to pure water than to spirit-of-wine. . . .



Figs. 10 and 11 from Nollet's classical paper (see text).

In another series of experiments, described in the same paper, Nollet confirmed his belief that the bladder is more permeable to water than to spirit-of-wine. The experiments were patterned on that of de Réaumur mentioned above:

"The experiment showed me," wrote Nollet, "what I had quite well predicted: I took a type of recipient, or a vessel open above and below; I covered the upper orifice with a piece of moistened bladder which I fastened tightly with twine bound down in several turns and which I left to dry until it became as though glued to the edges of the vessel. I put this recipient, so prepared, on an oval plate which was covered with moistened hide, *AB* (fig. 11), beneath which was a tube that terminated in *C* and *D* and that communicated with a pneumatic machine through the medium of the cock, *E*. On the other end of the same plate I put a small recipient, in the interior of which was enclosed the reservoir of a barometer *FG* . . . ; by means of this apparatus I could tell by how much I had rarefied the air in the recipient, *D*, because it communicated with that of the barometer, *G*.

"Having then rarified the air by one-half, the bladder of the vessel, *D*, was thrust inward a little and took on the shape of an inverted skull-cap, into which I poured water until it was about full. After some minutes the under-surface of the bladder was examined; I saw that the water had begun to leak through and that, little by little, it formed drops that fell from the lowest part: I counted 15 of these drops in the interval of 12 minutes.

"Without changing any part of the apparatus, I mopped, with a sponge, the water that remained on the bladder and I substituted it with an equal quantity of spirit-of-wine. . . . I waited fruitlessly for 10 minutes, when one drop fell, and, having re-admitted air into the vessel and examined the lower surface of the bladder, I found nothing but a light dampness that appeared to me nearly tasteless.

"It thus appears from this that the moist bladder offers passage to water which it refuses, almost entirely, to spirit-of-wine and that this latter liquid, in uniting with the water which it draws, so to speak, into the vial, makes it impossible for the water to exit through the route it entered even though its departure is invited by the tolerably strong pressure."

These fundamentally important observations of Nollet remained dormant for several decades. In 1815, F. Parrot recognized that all miscible fluids, when in contact, tend to wander into each other by "the affinity of the first order." Parrot did not mention Nollet and claimed to have been the first to discover this force, which he could not name. He pointed out that the process occurs even better without a membrane and thus realised the essential identity of osmosis and diffusion.

Again, osmosis became buried. It was re-exhumed by N. W. Fischer (1822), who observed the rise of a solution, in a glass-tube, which was separated from the solvent, water, by a piece of pig- or ox-bladder. He noted that, after a while, the level of solution in the

tube stayed constant; he also found that a very thin membrane, such as the allantois, permits relatively rapid passage of water. He admitted that the significance of the passage of fluids through animal membranes was more difficult to assess than would be expected at first glance.

The differential permeability of membranes and its sequence, osmosis, was now in the limelight. The first extensive and quantitative study of osmosis was that of the marquis de Néons, René Joachim Henri Dutrochet (1776-1847). Dutrochet was a physicist but mainly a physiologist and physician; he wrote at least two treatises on anatomy and physiology, was physician-in-chief to the Hôpital de Burgos, and was elected member of the Académie des Sciences of Paris in 1831. In his first paper on osmosis (1827) he stated that:

> When two liquids of different density or chemical constitution are separated by a fine and permeable partition, two currents, directed in an opposite sense and inequal in force, become established across this partition. The result is that more and more liquid accumulates on the side toward which the stronger current is directed. These two currents exist in the cavernous organs which form the organic tissues and it is these currents which I have designated by the names of *endosmosis* and *exosmosis*. My experiments have shown me that this phenomenon is not produced exclusively by organic membranes. Very fine inorganic plates produce it too. . . .
>
> This process continues to occur until the difference in pressure that the two liquids exert by reason of their height is equal to that of the attractions exercised by these two liquids on the column of liquid contained in the capillary tube. . . .

He explicitly stated, for the first time, that endosmosis must be an important biological phenomenon but no examples were advanced to support the claim:

> The more one advances in physiological knowledge the more motives one has for disbelieving that the phenomena of life are essentially different from physical phenomena: this opinion, which the authority of Bichat has above all contributed to establish, is indubitably erroneous" (Dutrochet, 1827).
>
> This process [*endosmosis*] is truly the fundamental activity of life. . . . The applications of these discoveries to Physiology are so direct and so evident that it is impossible to overlook them or, at least, to voluntarily close one's eyes to them. One casts a bird's eye-view on the general theory of life (Dutrochet, 1828).

By finding that osmosis does not depend upon membranes derived from animals or plants, Dutrochet (1832a) removed a possible rampart for vitalism:

> The result of this experiment was that the slab of marble [*calcium carbonate*], which was four centimeters in diameter, did not lose by filtration, at the end of one day, but the slight quantity of water capable, by subtraction, of depressing the water-level in the tube by one and a half millimeters. I put sugared water in this osmometer and then plunged the reservoir into pure water: there occurred entirely no endosmosis. I reduced the thickness of the slab of marble to one and a half millimeters; in this state it lost by filtration, in the interval of a day, eleven millimeters of water as measured in the tube. The permeability of this slab was augmented, as one sees, to a very sensible extent meanwhile the endosmometer which is closed was filled with sugared water and there was entirely no endosmosis. I reduced the thickness of the blade of marble to one millimeter. In this state it lost by filtration, in the interval of a day, twenty-one millimeters of water as measured in the tube. I put, in the endosmometer which this blade of marble closed, the same sugared water which I had used in the preceding experiments and the density of which was 1.12; I obtained an endosmosis which manifested itself by a rise of seven millimeters in twenty-four hours. This last experiment showed me that carbonated chalk is by no means totally deprived of the capacity to produce endosmosis, as I had found until then. I desired to compare this blade of marble with a piece of bladder of the same surface-area from the double standpoint of their permeability and their endosmotic property. Having, then, removed this blade of marble which closed the osmometer, I replaced it with a piece of bladder and measured its permeability to pure water in the same manner as below. I found the permeability to some things quite similar to that of the blade of marble of one millimeter in thickness.

Dutrochet (1832b) recognized that the organic membranes he used were not strictly impermeable to the solutes:

> In fact, in the somewhat protracted experiments, the organic membrane that closes the endosmometer does not at all conserve the same degree of permeability, with the result that endosmosis experiences variations which are altogether independent of the physical or chemical qualities of the liquids that are under experiment. . . . To obviate as much as possible the inconveniences mentioned above, it is necessary that the successive experiments performed with the same endosmometer be of short duration; it is necessary, furthermore, to repeat the experiments with the object of establishing, from their results, an average which cannot come short of being very close to the truth.

Similar experiments were performed by Magnus (1827), Jerichau (1835), Matteucci and Cima (1845), and, in 1849, by Ludwig himself. Matteucci and Cima used several animal membranes: skins of the frog, eel, and torpedo, urinary bladders, and the stomachs of various mammals and birds. The membranes were used, both when "fresh" and decomposed, mainly with the view of finding whether differences in permeability exist depending upon the direction of the osmotic current with regard to the surface of the skin: external and internal. Some quantitative differences were noted but it is doubtful whether the results are of any present value. They also confirmed previous findings that salts and sugar will diffuse out through the membranes (exosmosis).

3. Of the constituents of the blood, the glomerular membranes are impermeable only to the proteins, the fats, and to any minerals that may be bound to the proteins and fats. That fat occurs everywhere in the body as an emulsion of small droplets of 1/40 to 1/200 mm. in diameter, and even smaller, that the smallest reach the dimensions of Brownian molecules, and that "they also show molecular movement and allow so little light to pass that the masses formed by them, e. g. the fat of insects, appear almost opaque," was first enunciated by Ferdinand Moritz Ascherson (1798-1879) in 1840.[1] The particles of fat were recognized as being much larger than molecules and it was pointed out that the vitelline globules are droplets of oil; it was also stated that "As nearly all the fluids of the animal body contain albumin, an oil drop cannot remain in them for an instant without surrounding itself with a cell; nor can it divide into several, be they two or a hundred, without causing the formation of as many new cells." From Ascherson's remarks, one cannot wonder that Ludwig assumed that the glomerular membranes are impermeable to the fat in the plasm.

As to proteins, we have the statement of Ludwig (above) that Brücke (inaugural thesis?) had made the very important observation that the membrane directly beneath the egg-shell is impermeable

[1] I am much indebted to Dr. Elmer O. Kraemer of The Biological Foundation of Newark, Delaware, for informing me about this important paper by Ascherson. I am also obliged to Dr. Kraemer for other helpful notes (personal communication, April 20, 1942).

to proteins. Aside from this, the Dutch chemist Gerard Jan Mulder (1802-80), with whose work Ludwig was familiar, had recently published (1838) his results on the elementary analysis of proteins in egg-white and serum. According to Mulder, the formula for serum-protein is $C_{400}H_{620}N_{100}O_{120}SP$; the "atomic" weight was correspondingly large. The other proteins had practically identical formulae except for the number of atoms of sulfur and phosphorus, which were considered to be loosely attached to the main protein-"atom." Mulder and Scherer found that the basic formulae of "albumen," fibrin, casein, "tendons," chondrine, "hair," "horn," and "arterial membrane" (!) are nearly identical (cf. Liebig, 1842).

4. *Minerals can be bound by proteins and fats, i. e.* by substances held in solution by weak forces. Tobias Lowitz (1790-3) decolorised and purified water, i. e., removed the organic material, by shaking it with wood-charcoal and then filtering. Figuier (1811a and b, 1813) improved on this by showing that animal-charcoal, from the bones of large animals, was more efficient in decolorising wine than vegetable-charcoal. Guilbert (1812) decolorised honey by shaking with bone-charcoal and did not mention Lowitz or Figuier. In 1830, Thomas Graham tested the action of animal-charcoal on known saline solutions and found that silver chloride was taken down completely from its solution in ammonium hydroxide; lead acetate was also taken down but not copper sulfate. Mulder (1838) stated that the S and P of the protein-"atom" are bound to a quaternary organic body ($C_{400}H_{620}N_{100}O_{120}$) and indicated that the protein could be relieved of these minerals without extensive disruption of the protein-"atom." Ascherson's remark about the binding of protein by globules of fat has been quoted because it may have had some influence on Ludwig. Particles of protein were recognized as uncommonly large (see above). Ludwig could not have been slow in drawing a resemblance between the large particles of protein and fat and those of finely divided carbon.

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MAURICE ARTHUS' PHILOSOPHY OF SCIENTIFIC INVESTIGATION

PREFACE TO *DE L'ANAPHYLAXIE À L'IMMUNITÉ*, PARIS, 1921

TRANSLATED FROM THE FRENCH, WITH AN INTRODUCTION BY
HENRY E. SIGERIST

FOREWORD BY
WARFIELD T. LONGCOPE

FOREWORD

It is now more than 20 years since the French physiologist, Maurice Arthus, published a book, the title of which was "De l'Anaphylaxie à l'Immunité." At that time the monograph was a notable contribution to the subject, for Arthus was one of the pioneers in this particular field of investigation. His book is not a review of current information upon the subject, as he takes pains to point out, but the record of a direct experimental attack upon the problem. This starts with his original observations upon the reaction to repeated injections of horse serum in the rabbit; and, since the "Arthus Phenomenon" and the "Anaphylaxis" of Richet are two phenomena of fundamental significance, the text remains historically important.

There is, however, another reason why the treatise should not be forgotten, for it is introduced by a preface which is as fresh and appealing today as it was at the time it was written. An explanation for this preface is to be found in an interesting little circumstance that led Arthus to write the monograph itself. He received a letter one day from a young physician asking, "Mais qu'est-ce donc que l'anaphylaxie?" Arthus thought the question could best be answered by preparing an account of his own experiments; and as an introduction he wrote an essay upon the philosophy of scientific investigation.

This intimate and charming address of the master to his pupils

is a bit of medical literature which is worthy of being preserved. There is certainly nothing novel in the topic, but Arthus approaches it in such an unusual manner, and with such full understanding of the pitfalls that lie in the path of the unwary student, that the essay acquires a unique quality. In its own way it compares well with the celebrated "Introduction à l'Etude de la Médecine Expérimentale" of Claude Bernard, though Arthus has condensed what he has to say in comparatively few pages. He says this, however, in beautiful French, with feeling, "esprit" and great wisdom.

The book is now difficult to obtain in this country, for it is not to be found in some of the largest medical libraries. For many years it has seemed desirable that this delightful preface should be better known. A translation was contemplated but never materialized until the suggestion was made to Dr. Sigerist. With his quick appreciation and enthusiasm he immediately consented to undertake this rather delicate and difficult task, and now through his kindness it is possible to make this unique piece of medical literature readily available. It is hoped that all who read it may derive pleasure and profit from it.

WARFIELD T. LONGCOPE.

Introduction

Maurice Arthus has told us how he became a physiologist.[1] When he was a young student at the Sorbonne in Paris he used to walk up the hill between classes to the Bibliothèque Sainte-Geneviève. There one day he found two small volumes, unpretentious, poorly bound, covered with dust. They were the *Leçons de physiologie expérimentale appliquée à la médecine*, the course that Claude Bernard had given at the Collège de France from 1854 to 1855. He opened the book, looked at the first pages absent-mindedly, as you glance at a novel hesitating whether you should read it or not. But then:

> " my whole self was captured by the presentation of the great physiologist. I read the book without skipping a line, without skipping a word and—unheard of event for the conscientious student I was—I missed my next class. What a grandiose revelation this study of Bernard on glycogenesis! What life, what action! Experiments, hypotheses and discussions, new experiments, new hypotheses following one another in breathless succession, and a harvest of facts following closely the blossoming of hypotheses. This was no longer one of these cold, academic, monotonous and soporific scientific treatises to which, alas, I had been so often subjected. It was life itself with its action, its struggles, its triumphs. From that first contact on, I was forever in the grip of the experimental method and had faith in its almightiness. I closed the book, a physiologist."

Maurice Arthus came from Anjou, one of the most beautiful provinces of France to which he always remained deeply attached. Born in Angers on January 9, 1862, he studied in Paris in the early eighties and graduated in 1886.

Claude Bernard had died a few years before, in 1878. His personality and work had impressed the whole period with an indelible stamp. He had not only made great discoveries but had developed the experimental method into a tool that seemed apt to open the most

[1] La Physiologie, in the series *Les Sciences d'Aujourd'hui. Méthodes. Résultats. Hypothèses.* Paris, 1920, p. 1 f.

secret recesses of nature. He had endowed a whole generation of scientists with boundless courage and optimism.

Claude Bernard's influence reached far beyond the limits of science. His experiments at the Collège de France were attended by philosophers, historians, and theologians. The oriental scholar Ernest Renan declared history a science like chemistry and wrote not only a history of the origins of Christianity in many volumes, but also a book on the future of science. The historian Hippolyte Taine endeavored to interpret the history of art in scientific terms, and once went so far as to say that vice and virtue were products like vitriol or sugar. Emile Zola wrote "experimental novels" in which he put individuals of different constitution into a given environment, let them act and watched what happened. In 1880 he wrote a treatise *Le roman expérimental* that was inspired by Claude Bernard's *Introduction à la médecine expérimentale* and in which he discussed the application of principles of physiological research to the writing of novels. Physiology appeared to that whole generation as the queen of all sciences, because it was lifting the veil from the mysteries of life. And to the French, physiology was embodied in Claude Bernard.

Another great experimentalist was exerting at that time a tremendous influence on the generation of Arthus: Louis Pasteur who in those years was at the height of his career. Arthus speaks of the "Pasteurian epic" as a "hymn sung to the glory of the experimental method." Claude Bernard had shown how complicated physiological problems could be solved experimentally, and Pasteur was demonstrating year after year the immense practical value of the method.

A chemist by training who intended to devote his life to research in organic chemistry, Pasteur was driven by circumstances into most different fields. Whatever problem was set to him he approached without a preconceived idea, observed facts, made hypotheses, tested them in experiments, interpreted the results, and drawing the practical consequences from his studies made his immortal contributions. His work was so inspiring to the young generation because it seemed to demonstrate the "almightiness" of the experimental method.

Following the tradition of Claude Bernard, with Louis Pasteur as an example, Maurice Arthus became an experimental physiologist. In 1890 he was chef de conférences physiologiques at the Sorbonne. In 1896 he was appointed professor of physiology at the University of Fribourg in Switzerland. In 1900 he was for a few years chef de laboratoire at the Institut Pasteur in Lille, and in 1903 he accepted a chair at the Ecole de Médecine of Marseilles. And then, in 1907 he was called to the chair of physiology of the University of Lausanne, in Switzerland, where he established a permanent residence. For twenty-five years he was the center of the faculty, an inspiring and venerated teacher whose classroom was crowded not only with medical students but with students from all faculties who came for the joy of listening to him.

He was a physiologist of the old school equally at home in experimental normal physiology, biochemistry and pathological physiology. One of his early books was on the coagulation of blood, lymph and other liquids of the organism.[2] Another dealt with the nature of enzymes.[3] Most famous were his studies on anaphylaxis,[4] a field in which he made some of the pioneering experiments.

A man who was such a great teacher could not fail to write textbooks. His *Précis de physiologie* first published in 1921 went through new editions every few years and was the authoritative textbook in all French-speaking countries. The same is true of his *Précis de chimie physiologique* that had eleven editions from 1895 to 1932. In 1921 he published a third textbook, *Précis de physiologie microbienne.*

Every physiologist who is more than a technician is something of a philosopher because he is constantly dealing with the problem of life, and sooner or later he will feel the urge to step out of the laboratory and to look at the field as a whole. Arthus did it in 1920 in a book called *La physiologie* that was part of a series: *Les sciences d'aujourd'hui, méthodes, résultats, hypothèses.* He did it in a number of addresses and papers of which the following preface is one.

Arthus was a most eloquent speaker who had a superb command

[2] *Coagulation des liquides de l'organisme*, Paris, 1894.
[3] *Nature des ensymes*, Paris, 1896.
[4] *De l'anaphylaxie à l'immunité*, Paris, 1921.

of the French language. He was forceful by being colorful, piling up synonyms, making picturesque comparisons, developing an argument in a slow *crescendo* until the acme was reached and the point was hammered into the audience. When he wrote on general subjects he wrote as he spoke, and the reader of the following preface will immediately notice that this is an address, that Arthus is talking, talking to his disciples, warning them against pitfalls, entreating them to follow the right path.

When we read Arthus' scientific books and papers, we are astonished to find that they are written in a totally different style, simple, sober, matter of fact, yet never dull. The facts lend color to the picture and words are not needed—the facts and the clarity of their presentation. Clarity was a Latin virtue that Arthus cherished above all.

The following preface is a late document of the great French school of physiology. Before presenting the results of his experiments on anaphylaxis, Arthus felt the need to discuss the methods he had used. They were the methods he had inherited from Claude Bernard and Pasteur, the methods he wished to pass on to his students. His horror of theories was easy to understand at a time when vitalism was revived in Germany.

Arthus had faith in science. He was well aware that science could not solve all the riddles of the universe at once, but he was not impatient and considered it the duty of the honest scientific worker to contribute his share, modest as it might be, to the establishing of some new facts. In 1920 he wrote:[8]

> "Physiology is still incomplete and imperfect. Many points are still dark, many hypotheses still have to be justified. And yet the well observed and well established physiological facts are sufficiently numerous to provide medicine and hygiene with a solid foundation upon which these two sciences may build safely; and sufficiently numerous to provide a scientific philosophy with general views on the conditions and mechanisms of life.
>
> Strongly impressed by the great results obtained, some peo-

[8] *La Physiologie*, p. 427.

> ple have thought that all manifestations of life, even the most immaterial, should belong to the realm of physiology. We believe this to be a mistake and think that it is important to separate clearly the material or physiological facts from the immaterial or psychological ones. This undoubtedly will reduce the field of physiology but it will remain vast enough and there will be enough virgin soil left to provide work to honest researchers for years and perhaps centuries."

Our young people who are at the beginning of their scientific career, who have taken the heroic resolution to devote their life to research will, I am sure, find inspiration and encouragement in the words of Arthus. His honesty, his fanatic devotion to science, his insistence upon originality and last but not least his method, still the most promising one today, will provide them with guidance and will renew their faith in the dark hours of discouragement through which every researcher must go.

In preparing this translation I endeavored to preserve the style of Maurice Arthus as much as possible without violating the English language. The difficulties were numerous, and I am much indebted to Dr. and Mrs. Warfield T. Longcope for valuable help and many suggestions.

HENRY E. SIGERIST.

MAURICE ARTHUS' PHILOSOPHY OF SCIENTIFIC INVESTIGATION

Preface to *De l'Anaphylaxie à l'Immunité*,
Paris, Masson et Cie, 1921.

This book contains the sum total of the experimental results that I have gathered during the last twelve years on anaphylaxis, proteotoxicity, snake poisoning, anaphylaxis-immunity, and anti-venom serums. Most of my researches have already been expounded in notes presented to the Academy of Science and the Society of Biology, and particularly in memoirs published in the *Archives internationales de physiologie*. I found it necessary to weld them into a homogeneous whole in order to assign to each of its constituent parts its relative value, its accurate significance, the place it takes in the long series of facts which lead from the study of anaphylaxis to the study of immunity.

Besides, in publishing this book I am fulfilling one of the basic duties that I have assumed as a professor. Indeed, the university professor of physiology must not only teach. He must not only engage in original research intended to advance science. He must also endeavor to provide the young people who are emerging to scientific life, the physiologists, biologists, physicians—our students of today, our successors of tomorrow—with clear and precise directions that will enable them to avoid the hesitations, the gropings, the disappointments, the errors, the discouragement, all those miseries of the beginning of a scientific career. He must provide them with directions that will guard them against hasty generalizations, *a priori* assumptions, brilliant theories. The young people are unaware of the treachery of these brilliant theories, and with all too generous enthusiasm admit them to the inner circle of their scientific life, just as they, by the way, admit to the inner circle of their private life the brilliant companion who has seduced them by his *esprit* but who only waits for an opportunity to deceive and betray them.

Those who will read this book and will take the trouble to think it over, will find in it such clear, firm, and vigorous directions or, at least, I hope so. Oh, my book, without any doubt is neither complete nor perfect; it is the work of a human being. I find rather numerous gaps in it and feel that it has many weak spots. My readers, undisturbed by the vanity of an author, will find many more than I could. But I think they will find the manifest sign of a continuous, tenacious and strong effort not to commit certain mistakes, not to fall into certain errors. I shall say more about it in a moment.

" The experimentalist," I once wrote, " has observed a fact. A fact is always interesting. But just as a work of art acquires all its value only if it is properly placed and properly lighted, a fact acquires all its value only if it is properly interpreted. Hence the experimentalist attempts such an interpretation, that is, he makes a hypothesis. Such a hypothesis obviously has no objective value. In order to give it a value, the experimentalist thinks out an experiment, that is, he creates the conditions required for the observation of a new fact which must establish the value of the hypothesis. The new fact leads to a new hypothesis and thus from experiments to hypotheses and from hypotheses to experiments the physiologist progresses in the cognition of the mechanism of life."

In this book one will find the practical application of this working method which is eminently simple and infinitely fruitful. Indeed, the first observation raises a question which is the hypothesis suggested by it. An answer corresponds to this question and is provided by the experiment conceived for its solution. A new question is followed by a new answer and so on, just as one proceeds in the catechism. And this leads to the cognition of facts.

To cognize is really the appropriate term in this connection, for in the pursuit of scientific work it is not enough to see and still less to perceive; one must cognize, that is observe with the most vivid attention, ascertain with the most rigorous precision. And to this end one must, as far as possible, measure and consequently assign a number to the fact observed, a number that will define its quantity and will permit one to determine its relations to other facts of the same nature.

The physiologist must also group the recognized and measured

facts and must classify them; otherwise there is disorder and anarchy. Disorder and anarchy, moreover, are just as dangerous and detestable when they reside in the laboratory as they are when they reside in the government. The zoologist and the botanist classify in their collections the specimens of animal and vegetable species that they have gathered or collected. In the same way, the physiologist classifies the facts he has just observed, in the collection of facts previously published. He proceeds to this end by making collations and comparisons by means of which he determines the similarities and dissimilarities of the old and the new facts. He, besides, makes a distinction between fundamental and accessory facts putting the first in full and bright light while letting the others remain in dimness or darkness, just as in a museum of natural history certain specimens are conspicuously in the foreground while others are buried in a dark corner. The classifying and placing of the facts as I just described, is called in physiology determining the signification of the facts.

There is a capital difference between the fact and its signification: the fact has an absolute value, provided it has been well observed and its determinism has been rigorously established; its signification has but a relative value. Indeed it depends, at least to a large extent, on the mentality of the biologist who has suggested it, on the studies he has made, on the researches he pursued in the past and those he is pursuing at the moment, on his knowledge of scientific literature, on the people he meets, etc. The fact is accepted by all: its accurateness can be verified easily when one possesses the means to do it and when the conditions that produce it have been evenly and accurately specified. The signification, however, may vary with different scientists just as in a museum of natural history the grouping of specimens may vary with different curators. A specimen may often deliberately, or because circumstances call for it, be placed quite legitimately in one group or another or may within a group be placed closer to one or another specimen. The same is true also for biological facts. Summing up we can contrast the rigidity of the fact with the plasticity of its interpretation.

We have established the signification of a fact observed; in doing this we have performed a highly personal act as I have pointed out

expressively. Hence we may have erred, blinded as we all too often are, in our judgments. A strict control is imperative. This control we find in the criticism called forth sometimes by the publication of our results, but we may already find it in the criticism which we ourselves raise against our conclusions, and we shall specify the value of such criticism by reasoning and experimentation.

I have been told that Claude Bernard, whenever he had reached some conclusion, used to criticize it, firmly determined to demolish it if it was ever possible. When in spite of all his efforts he did not succeed in pulling it down, then and then only, did he accept it as valid and did he publish it. Thanks to this wise rule to which he adhered quite generally, the great physiologist has left a life-work behind that has resisted the destructive forces of three quarters of a century. Could we say that much of the work of those physiologists who thought they could dispense with this indispensable control? What survives of it as a rule, beyond a few scraps?

Let us follow up our comparison: the zoologist has received a specimen. He has classified and has displayed it in his collection in a place more or less conspicuous according to the importance it seems to present. But he is not satisfied with one specimen; this might well represent an anomaly within the species or at least a variation. Certain characteristic traits might be predominant in it which are attenuated in the majority of individuals of the species, or vice versa. The collector, therefore, sets out searching for a certain number of specimens, individuals, belonging to the same group. He puts them next to the original specimen, and now he can give a description that applies to all individuals of the same species without running the risk of making a mistake. To this description he adds a note on the different variations if this seems advisable. The biologist imitates him; he is not content with one single experiment to obtain an answer to a question that has been stated as a hypothesis. He repeats the experiment in a series of animals and carefully records the essential results and the variations of detail. And this he repeats until the sum of experimental manifestations constitutes a solid, homogeneous whole in which the elements differ by mere shades. Should there be some discordant result in the series of tests that he has just conducted, he would carefully beware

of suppressing it. He would seek its cause in some difference in the conditions under which the observation took place, and this might possibly lead him to ascertain some important facts. Besides, if he should not succeed, he would conscientiously record this divergent result so as not to lose track of it, just as the zoologist carefully preserves abnormal specimens in a special container. The development of the experimental investigation often gives a simple solution to the little puzzle raised by the special case.

After having multiplied the experiments the biologist must apply himself to generalizing. In studying an animal species the zoologist has found a characteristic feature which seemed to present some interest. He searches for it in the neighboring species of the same group and in the species of neighboring groups and beyond this; and according to whether this characteristic is peculiar to the species under examination or whether it also occurs in other species, he attributes to it more or less significance, at least from a statistical point of view. The biologist cannot proceed differently: he has observed a fact; he has interpreted this fact, after it had been well established by a series of concording experiments and observations. It is important now to know how frequently this fact occurs, not only in the field under investigation but also in neighboring fields. After having applied all his attention to the problem of interpretation, which is a matter of quality, the biologist does not neglect the problem of generality which is a matter of quantity.

In order to ascertain the value of a hypothesis, we launch an experiment and, as we said before, we repeat it many times. This may be enough if the experiment was well conceived and if its results are clear and precise. But even in this case it would be a mistake to disregard the mass or quantity factor. The conclusion that we have reached acquires undoubtedly much more value and is accepted much more readily and favorably if we arrive at it in several different ways. Hence, it seems to be advantageous at least, to answer the hypothetical question through several series of experiments conceived on different plans—when our imagination permits us the treat of such a scientific luxury. It is a luxury, of course, but it is quite good to be able to be lavish occasionally, even in science.

By endeavoring to generalize too much, however, one may run

the risk of making a mistake which would consist in attributing exclusive importance to quantity. By this I mean a mistake that would consist in being satisfied with a superficial study, a cursory inspection of numerous facts or of groups of numerous facts without examining carefully and in detail at least one of them. Let me repeat that the conclusions drawn from a scientific investigation are solid and lasting only if they are based on as complete as possible a study, accurately and minutely conducted. In order to avoid this mistake, it is necessary, after having surveyed the field of a rather broad territory, to dig deeply and perseveringly there where according to our previous summary examination we may expect the greatest accumulation of scientific treasures. It is good to find the different veins of a mine, but it is better to exploit one thoroughly; the others constitute reserves for the future.

In generalizing, moreover, provided it is done carefully and methodically, one frequently gathers particularly useful data: one picks here a detail, there a peculiarity, there finally an anomaly which in the future may prove eminently helpful in solving some of the problems that the experimentalist will have to face.

Observe facts, conceive a hypothesis, determine its value through one or several series of judiciously instituted experiments, give the interpretation or more accurately one interpretation of the facts and ascertain the excellence of this interpretation through strict criticism; generalize the results experimentally without forgetting that an investigation must be pushed to the end—these are the directions that I propose to young people on entering the scientific career.

Some among us, however, are not satisfied with observing facts, with establishing their conditions, with giving their interpretation or even several interpretations. They wish in addition to foresee new facts before they are in a position to recognize them. They wish to interpret them in advance before they have even observed them. They choke within the boundaries of the Known and need the infinite space of the Unknown in which to breathe freely. Then they promulgate a theory, a kind of philosophic system, designed to group, mostly artificially, the known and unknown facts in the same category or in several related categories; designed to provide a dogmatic interpretation, as it were, of these facts, making them

agree with the *a posteriori* demonstration of a doctrine that was conceived *a priori*.

In certain scientific circles one professes a boundless admiration for the Theoreticians. They are considered infinitely superior to the Experimentalists. They have elevated themselves above the materiality of science and float in the sphere of ideas. Glory to them! I have a different opinion. I consider the theoreticians extremely dangerous individuals, and I believe that we must arm and defend ourselves against them vigorously. This is why:

There cannot be any disagreement among observers about the facts themselves. Whether we ascertain a fact by means of our sensory organs or by means of special instruments appropriate to manifest, record or measure it, the fact cannot differ from one observer to another, provided the examination is made under rigorously determined conditions. The fact is categorical, absolute, peremptory.

The interpretation of the fact observed may vary according to the researcher who has established it. Hence there may be some discussion about a stated interpretation which is submitted to the approval of the scientific world—discussion, yes, but not a quarrel, not war, because one does not fight for a classification. Now, discussion may lead to progress, to the light, when it takes place among men who possess certain intellectual and moral qualities. At the end of a discussion one often arrives at a solid conclusion that is no longer opposed. Sometimes, undoubtedly, we must resign ourselves to making some kind of a compromise which, however, can be accepted by every one without offense to his self-respect. Let me repeat that it is merely a question of classification and nobody would dream of sacrificing his equanimity, his property and life in order to prove the superiority of a classification.

Things are totally different with theories. A theory is a dogma, based on some arguments of faith. Does it correspond to reality, to truth? Perhaps, but we are never sure about it. We accept or reject it for reasons which in most cases are purely personal and are not always exclusively scientific. In accepting it we perform an act of faith and in rejecting it we perform an act of doubt. Performing an act of faith, however, involves the entire man up to and includ-

ing his conscience; and to persist in one's faith becomes in a sense a question of honor. Oh, I know: one says and repeats that the theory is only provisional and that one is ready to abandon it as soon as facts will have demonstrated its inaccuracy etc. But in reality, those who repudiate a theory that they had once proposed, or a theory that they had accepted enthusiastically and with which they had identified themselves, are very rare. The great majority of them shut their ears so as not to hear the crying facts, and shut their eyes so as not to see the glaring facts, in order to remain faithful to their theories in spite of all and everything.

And then, the theories—I mean the great theories—go beyond the boundaries of the laboratory. They are usually announced in learned societies, in academies, in scientific periodicals. The daily newspapers, magazines of the most different kind entertain their readers with them in glowing language. Lecturers talk about them to their audiences in high tones. Government authorities give formal approval and extend official congratulations. The theoreticians find themselves in the limelight of publicity. How could they change their opinion without losing face?

And then we often see a performance which is pathetically sad. The theoretician who is not necessarily a man without scientific merit when he condescends to experiment—the theoretician becomes like the attorney who defends a client in spite of the evidence of his crime, like the politician who exalts his party even for its mistakes and vile actions which he proclaims to be acts of virtue and of courage. The theoretician automatically sorts the facts newly brought to light; he retains those, even the most modest ones, that seem to prove him right and neglects the others, even the clearest, most precise and convincing ones if they appear to indict him. Blinded by his passion, that is, by his immoderate love for his theory, he has recourse to all means, honorable or not, in order to defend it, for to him all means have become legitimate. He has ceased to be a scientist and has become a partisan.

Seek facts and classify them—and you will be the workmen of science. Conceive or accept theories—and you will be their politicians.

One claims, it is true, that theories have at least one advantage,

and a considerable one, namely, to stimulate experimental researches intended to ascertain their worth; that theories thus evoke facts and therefore become useful to scientific progress in the highest degree. Hence, in spite of what I said before, I would admit theories though exclusively as a working method, and only for old experimentalists who having seen so many theories collapse miserably are profoundly skeptical. But I would not admit them for young scientists who all too often accept them as a revealed truth and make the positive facts bend before the majesty of the dogma. I would accept theories if we had no other less dangerous and equally productive method of research, capable of replacing them in that particular function. But there is such a method: it is the one that I have pictured in broad outlines before. It consists in observing facts, in conceiving a hypothesis (a hypothesis is not a theory but simply a question), in ascertaining the value of this hypothesis experimentally, in interpreting the experiments, and in criticizing the interpretation vigorously and strictly.

In the book that I am presenting today, you will not find me expounding any personal theories. I have kept them away from my report mercilessly just as I have ignored them mercilessly during many long years of research. And yet my work contains many new facts, facts that the theoreticians had probably not foreseen.

The interpretations of the facts observed that I have proposed, have been useful to me in orienting my researches toward fertile grounds; yet I am aware that such classifications are relative and if it pleases my colleagues in biology to suggest others more suitable to their needs I shall have nothing to defend, nothing to safeguard, no polemic in which to engage, no counsel's speech to make, and consequently I shall not have to suppress or distort any facts. I shall be able to preserve without difficulty the equanimity necessary for scientific research. Could I, if I had built up a theory that somebody attempted to demolish? Would I not have to wage war? For war is being fought in the scientific field in defense of a theory, just as it is fought in the political field, in order to prove the superiority of a social doctrine, of a political system or even of a religious or philosophic idea. But no war is fought, so far as I know, to establish the excellence of a classification. I would even go further: if

the facts that I have discovered permit several interpretations, I could only rejoice, realizing thus their importance and value, for importance and value result from the multiplicity of possible uses.

Oh, of course, at the end of a day of experimental work during which I found facts that seemed interesting to me, I let my mind wander into the land of fancy and dreams and let it rove in the garden of illusions. But all this dissipated during the night and the next morning on entering my laboratory I had forgotten it. Thus acts the mother after a hard day's work: sitting at the cradle of her sleeping child, she dreams of the future of the babe, and a sweet smile lightens her face, when she sees the successive stages of his life evolve, of a life that must all be of joy, of happiness, of success and triumph. The next morning she resumes her daily task having become strict and serious again in contact with the realities.

Young men who read these lines, if you wish not to experience the bitterness of disappointments in science, do not let yourselves be seduced by the treacherous lure of theories. Young men, listen to the old experimentalist that I am, beware of theoreticians, beware of theories!

* * * *

In order to succeed in advancing the experimental science of biology it is not enough to follow a good working method; one must in addition possess certain moral qualities, at least to a certain degree, and one must make an effort to develop them more and more. This is in my opinion a very important point and I beg leave to explain it with more precision.

At the origin of many scientific discoveries there was an observation made by chance which the experimentalist grasped, dissected, interpreted, and discussed in order to wrest from it the secret it concealed. It was an observation made by chance that led Pasteur to the discovery of vaccines. It was an observation made by chance that led Ch. Richet to the discovery of anaphylaxis to the "congestines." It was an observation made by chance that led me to the discovery of sero-anaphylaxis and proteo-anaphylaxis. But chance, in biology at least, does not grant its favors to all and sundry. It seems to require from its protegees one quality, scientific curiosity.

He who possesses that mental attitude is not content with looking casually at the facts that turn up, and with giving them without further inquiry any kind of interpretation, the first that occurs to him. No, he examines the fact with sustained attention, repeats his examination as often as is needed to distinguish between the constant peculiarities and the variable elements. He describes, analyzes, measures, controls, criticizes, interprets and in order to justify his interpretation, conceives an experiment that will demonstrate its worth or its emptiness.

When I was a student at the Sorbonne my old physics teacher, old Desains, as we used to call him, told us an anecdote that strongly impressed me. It seems that one of the most famous German chemists had observed a reddish liquid that appeared as a residue of I do not know what chemical preparation and that emitted strongly irritating vapors. Without spending time in studying it or even in making a cursory examination, the famous scientist decided that it was iodine chloride. Balard who from a scientific point of view was very much inferior to the German chemist—at least in the opinion of old Desains—observed the same substance as residue of the same chemical preparation, by chance also, like the German chemist. But Balard possessed that scientific curiosity of which I am talking at the moment: he took the liquid, examined it, made various tests with it, and ascertained that its properties differentiated it from other known chemical bodies. Thus he was induced to consider it a new body which he found to be an elementary body. Balard in his curiosity had discovered bromine and by this very curiosity had revealed himself—I apologize to my old teacher for contradicting him—infinitely superior to the German chemist from a scientific point of view.

The experimentalist must have a straight, clear, and precise mind, and these qualities must appear in the choice and limitation of the project. They must also appear in the statement of the hypothesis, that is of the question being asked, and in the conception of experiments, that is in the preparation of the answers.

An observation has been made which may cause a series of hypotheses or questions, orienting research in various directions.

The experimentalist will select one, one only, the one that seems to hold the greatest promise of results or seems easiest to solve. He will discard all the others, at least for the time. Thanks to this procedure one single question will be raised to which he can devote himself entirely. He will strictly limit his subject and will establish its borderlines with precision so as to avoid being driven into sidelines that would turn him away from the essential object of his research. He will hold to the principle of unity remembering the good old proverb: *qui trop embrasse mal étreint.*

The question raised must be such that it permits an answer, and that this answer may be clear and may if ever possible be expressed by yes or no. Ambiguous, approximate answers, full of reservations and double meaning are not conducive to progress and must be condemned. But the question, of course, must have been put in a certain way. If a discussion remains confused it is not always because somebody answers in vague terms but often because the questions have been wrongly put.

To a question categorically put a categorical answer must correspond. Hence the biologist will endeavor to prepare for this answer by devising an experiment that is able to give it. It is impossible, by the way, to set a rule of conduct in this respect; it is a matter of clear and limpid imagination, a mental quality which you may possess in various degrees, upon which you may improve constantly if you are ready to apply yourself to it with iron determination.

A well outlined subject, a question clearly put, an experiment able to lead to a limpid solution, a categorical answer—these are some of the conditions required for a fruitful experimental investigation. This presupposes in the experimentalist the mental qualities that we call clarity and precision.

Among all the qualities that the experimentalist must possess, there is no doubt that none has greater value to him than tenacity. He has planned a series of experiments intended to determine the worth of a hypothesis; he carries them out but instead of finding in the results of these practical tests a plain, clear, and precise answer, he obtains nothing but approximate if not incoherent

results. He intended to solve a scientific problem by various methods in order to give his solution more stability and solidity, and now the methods employed lead to incongruous results or at least results that seem so. Will he let himself be discouraged, give up the game because difficulties have arisen? If so he should renounce the experimental career, for the path of the experimentalist is littered with obstacles that he must surmount by necessity if he wishes to progress and reach his goal. He only is fit to experiment who senses a rugged joy when he comes to grips with difficulties, who rushes headlong to solve them and will devote all his time, all his forces, all his energy and his entire soul to the task. He will first of all and to the end search for the cause of the experimental incoherences that have upset him so much, and he will almost always find that they are owing to lack of accuracy in some conditions of his experiments. With a little attention he will overcome this defect. He will examine his methods of research, will criticize them most rigorously, will scrutinize their qualities and shortcomings in order to eliminate those that have some flaw and that he had accepted too swiftly in the beginning. In most cases this will be enough to eliminate the obstacle, yet not always, and it may well be that the difficulty in spite of his care remains unsurmounted, perhaps unsurmountable. Should he give up his research, unwilling to tread indefinitely on the same ground? Yes and no. To continue working as he did before to no other end than landing in a blind alley or at the foot of a steep cliff would no longer be tenacity but stubbornness, and if tenacity is a virtue, stubbornness is a vice, or at least a fault. Hence the experimentalist will not persist indefinitely. But to avoid lack of tenacity that is to avoid committing a fault—fault of character—he will not definitely give up solving the problem; he will postpone its study for the time while keeping it always in mind. Since he was not able to attack the obstacle from the front, he will endeavour to circumvent it, and quite often he will succeed, sometimes soon because he conceived some ingenious device, sometimes after months and years during which he never forgot and because new facts opened up new paths along which he was able to progress and to reach his goal. It is rare that tenacity does not find its

reward—under one condition, however, namely that this tenacity be essentially active. By this I mean that the experimentalist ponder and meditate deeply over the problems raised, over the results obtained, over the experimental possibilities. Indeed it is not in the turmoil of social life, not through academic chats nor laboratory gossip that we come to see the light, that interpretations become clear, that experiments are conceived, and conclusions reached. It is through solitary, profound and sustained meditation. In order to make some progress in the experimental sciences one must meditate a great deal.

We have repeatedly mentioned in this outline the necessity of controlling the facts observed, of discussing the interpretations proposed and the meaning attributed to them in order to accept as true and valid only that which has stood the indispensable test of scientific criticism. This presupposes a special mental attitude which unfortunately is hardly developed in the schools, in the colleges and perhaps even in the universities, namely critical sense. This is the tendency of the mind to seek the true value of facts and results, of methods and concepts, the imperative need for strict control, abundant justifications, precise explanations, as a result of which we accept only those conclusions as final that have successfully resisted the attack conducted against them. The critical spirit, by the way, has nothing in common with the spirit of systematic opposition or with the spirit of disparagement. The critical spirit seeks the truth and hates above all the error; it is an eminently sound spirit. The spirit of systematic opposition takes the opposite side of every proposition, of every conclusion without endeavoring to ascertain their worth. The spirit of disparagement searches for evil everywhere and if necessary invents it where it does not exist. The spirit of systematic opposition and the spirit of disparagement are eminently morbid spirits. You will cultivate in yourselves the critical spirit which you can not develop strongly and vigilantly enough. You will tear out the two others, and if by chance they should some day bud on some old root that has not been exstirpated, you will carefully see to it that this shoot be cut as soon as it appears, just as the farmer does with thistles and weeds.

We have insisted before on the necessity of introducing into experimental research exact measurements that can be expressed in figures, and of not being content with approximations or superficial results. Now, in a biological phenomenon there are usually multiple manifestations concerning this or that function, this or that organ. In order to measure this phenomenon and to perceive its exact laws, it is necessary to select among the various manifestations those which lend themselves to measurement on the one hand and, on the other hand, those which may rightfully be considered representative of the phenomenon. Of course, we could choose arbitrarily any one of these manifestations but our research would then assume a purely empirical character which is not what we want. Hence we must first of all study the phenomenon which we endeavor to perceive and the measures of which we wish to find. We will change the various elements that may concur in the phenomenon under consideration, one after another—and there are usually many. We shall obtain results which must conform. We will not hesitate to make series of experiments, increasing progressively and regularly the variable factor and we will repeat the work over again, changing the conditions, each one separately or several at a time, whereby the others are kept strictly constant. This is labor that requires patience, meritorious patience, because the work is long, irksome, and often troublesome and because the conclusions come slowly and do not yield brilliant results that fill you with enthusiasm. But let us not forget that without patience there is no precise method and consequently no precise result.

Meritorious patience—for it presupposes relentless self-control. Here you have numerous ideas for experiments haunting you. Here you have the practical applications presenting themselves from all sides: the temptation to set aside temporarily the obscure and involved investigations is strong, imperative, tyrannical. You think you will come back to them later, and will fill the gaps after the work, more or less presentable, has been presented. In the meantime you conceal and hide them. It is so easy because the experts are very often satisfied with the apparent results. You are congratulated and may even cause some jealousies. But you know well

enough that the question of filling the gaps will never come up again. The man who had not the strength to put on the brake firmly, will never have the power required for going back. He has once let himself be carried away by the flood of ideas that beset him; having yielded, how could he resist later? And his work will be unstable because its foundations were too weak and too shaky; it will not stand the test of time. When it is necessary the experimentalist must be able to oppose a categorical, uncompromising and final no to his imagination. The experimentalist must possess full and entire self-control.

I have not the vain pretention to believe that I have thus traced the complete picture of the experimentalist. This is nothing but a first and very imperfect sketch but I think that it gives the broad outlines of the subject.

* * * *

The reader will probably find this preface very long and yet I beg his permission to add a few more remarks.

The young man who wishes to become an experimentalist, after having acquired at the university the classical basic notions of physiology usually joins the staff of a professor. He expects from him besides the hospitality of his laboratory, initiation into the methods of scientific research and training in biology. This he receives through the suggestions made in the course of intimate and frank discussions in the laboratory and through the example given by the professor in the pursuit of his physiological investigations. And often the young biologist, dominated by his teacher who may be a brilliant speaker and marvellous leader of men, dazzled by the burst of discoveries that follow each other precipitately, gripped by the forcefulness of practical applications that germinate, grow, flourish and bear fruit under the vivifying influence of the great biologist—I say, the young biologist endeavors to imitate his teacher in every respect; he tries to resemble him completely and strives to identify himself with him, to merge himself with him. His infinite admiration will deprive him of his intellectual independence and originality.

Sometimes also—the case is not so rare—the young man who says he wants to become an experimentalist, seeks first of all a means

to secure for himself an eminent scientific, or rather juxta-scientific, or even extra-scientific position. During his university years he has come to know the magnates of science; after careful consideration, without enthusiasm he has selected one to whom he attaches himself and who will be not his teacher but as the school language puts it so well, his Boss, the man whose influence he wishes to secure to serve his purposes, whereby he is willing to sacrifice all his independence, all his originality, willing to submit to anything if it serves the end.

And thus it happens that the two major qualities, the spirit of independence and the spirit of originality are suppressed and sterilized for a long time and without fail by the enthusiasts and by the careerists, for different reasons but with equal success. And this is why the scientific work of our young people today is often so dull, so colorless, and so sad. It lacks the characteristics that are those of robust health and a free life, namely spontaneity and unexpectedness.

I shall not waste words about the careerists. But to the others in whose hearts the sacred torch is lit, I cry as loudly as I can: young men, preserve jealously your independence and your originality! Honor your teacher, as is fitting, and respect him sincerely. But accept his directions only if they seem justified and only in so far as they respect your independence and your liberty. Follow his example wittingly only, that is only if it seems to you good, noble and worthy. If you discuss scientific matters with your teacher, ask questions, argue. Do not accept his words, all his words, without reservation and criticism. Criticize with moderation, of course, and first of all respectfully, but criticize firmly.

And if in order to preserve your independence, your human dignity, you experience sometimes troubles, difficulties and all that follow, preserve your independence in spite of all and preserve it fiercely. The day will come when you will congratulate yourself for having done so. Of course, you will not be granted official honors, social prestige and all the vanities which you would have bought at the price of freedom of thought. Be not affected nor depressed by it. The day will come when you will be infinitely happy about it.

Preserve your originality. It is the result of the gracious and beneficial influence that your parents, your friends, the people of your home town have exerted on you. In respect and gratitude to them, preserve your originality; you owe it to them.

Preserve your originality. It is this that will give your scientific work its frankness, its grace, its elegance, its warmth and life among so many artificial, banal, commonplace, cold, and corpse-like works, for originality—is the colorful bonnet of the girls of Anjou among the banal Parisian hats.

MAURICE ARTHUS.

THE ARISTOTELIAN AND THE MODERN UNIFICATION OF THE STRUCTURAL AND FUNCTIONAL ASPECT OF LIVING MATTER

HEINZ HERRMANN

The subject of the unification of the structural and functional aspects of living matter has been brought into the realm of Ophthalmology by G. L. Walls' recently published book [1] on the vertebrate eye, in which structure and function of the parts of the eye are described as dependent categories. The assumption of an independent existence of structural and functional principles has been restricted, by recent investigations into the molecular level of living matter, to a higher degree, than was the case at previous stages of modern research.[2] The results of these investigations suggest that the smallest structural unit of muscle tissue, the molecules of the muscle protein myosin, are also catalysts for one of the metabolic reactions which participate in the formation of chemical energy which in turn is essential for the performance of work. It seems that the myosin molecule changes its shape at the very moment in which it combines as enzyme with its substrate, initiating, thereby, the cycle of metabolic reactions which lead to restoration of the original state.

It seems therefore opportune to recall one historical instance, and probably the only one, in which structure and function have been perceived as an inseparable whole, i. e., the Biological System of Aristotle, in which the persistent unification of these entities is one of the foremost features. In fact, this unity was so self-evident to Aristotle, that structures which did not allow functional interpretation escaped his cognizance. It is only thus, that one can understand, for example, why the characteristic topography of the gray and white

[1] G. L. Walls, *The Vertebrate Eye and Its Adaptive Radiation*, Cranbrook Institute of Science, Bloomfield Hills, Mich., 1942.

[2] Engelhardt, W. A., Enzymatic and Mechanical Properties of Muscle Protein, *Advances in Contemporary Biology*, # 14, 177, 1941 (Russ.) Translated by P. Talalay in *Yale J. Biol. and Med., 15*: 21, 1943; Engelhardt, W. A. and Ljubimova, N. M., *Nature, 144*: 668, 1939; Needham, J., Kleinzeller, A., Miall, M., Dainty, M., Needham, D. M., and Lawrence, A. S. C., *Nature, 150*: 46, 1942.

matter in the brain and partition of the kidney into a medulla and cortex are not mentioned.

The insistence on a unification of structure and function with few exceptions is to be found throughout the writings of Aristotle. The position which he takes can hardly be better demonstrated than by quoting two typical examples from the book, *On the Parts of Animals*.[8]

. . . The duct which runs to the kidney from the great vessel does not terminate in the central cavity, but is expended on the substance of the organ, so that there is no blood in the cavity, nor is any coagulum found there after death. A pair of stout ducts, void of blood, run, one from the cavity of each kidney, to the bladder; and other ducts, strong and continuous, lead into the kidneys from the aorta. The purpose of this arrangement is to allow the superfluous fluid to pass from the blood vessel into the kidney, and the resulting renal excretion to collect, by the percolation of the fluid through the solid substance of the organ, in its centre, where as a general rule there is a cavity. (This by the way explains why the kidney is the most ill-savoured of all the viscera.) From the central cavity the fluid is discharged into the bladder by the ducts that have been mentioned, having already assumed in great degree the character of excremental residue. The bladder is as it were moored to the kidneys; for as already stated, it is attached to them by strong ducts. These then are the purposes for which the kidneys exist, and such the functions of these organs. (Book III, 9-671.)

. . . So far then this much is plain, that all animals must necessarily have a certain amount of heat. But as all influences require to be counterbalanced, so that they may be reduced to moderation and brought to the mean (for in the mean, and not in either extreme, lies the true and rational position) nature has contrived the brain as a counterpoise to the region of the heart with its contained heat, and has given it to animals to moderate the latter, combining in it the properties of earth and water. For this reason, it is, that every sanguineous animal has a brain; whereas no bloodless creature has such an organ, unless indeed it be, as the Poulp, by analogy. For where there is no blood, there in consequence there is but little heat. The brain, then, tempers the heat and seething of the heart. In order, however, that it may not itself be absolutely without heat, but may have a moderate amount, branches run from both blood-vessels, that is to say from the great vessel and from what is called the aorta, and end in the membrane which surrounds the brain; while at the same time, in order to prevent any injury from the heat, these accompanying vessels, instead of being few and large, are numer-

[8] *The Works of Aristotle*, Translated . . . under editorship of J. A. Smith and W. D. Ross, Oxford, Clarendon Press, 1912.

ous and small, and their blood is scanty and clear instead of being abundant and thick." (Book II, 7-652.)

The bulk of the descriptive material seems here divided qualitatively into two nearly equal parts. The discrimination applied is based on the nature of the structural correlate. The alternative use of structural correlate as morphologic descriptive notions and as material qualities should be noted. In the case of the kidney, it is the sum of the gross anatomical properties like the cave, the peculiarities of vascularization, the ducts and the attachment to the bladder. In the second case, however, it is that property of the brain which in Aristotle's terminology is synonymous with its quality.[4] The second alternative shows that Aristotle employed categories which were as close to the contemporary notions of chemistry as it was possible for him to come, considering his concept of matter as a non-atomistic continuum.

The unifying principles in Aristotle's Biology are the concept of the purposefulness of nature and that of a final cause. In some exceptional instances, however, structure does not appear to be predetermined by its functional correlate. These cases are none the less important since here Aristotle has to resort to the category of necessity.[5] Thus in the formation of the kidney fat, the colors of the eye, etc., structure becomes merely the necessary equivalent to the material and efficient cause, and at the same time its purposefulness for the sake of a functional correlate is lost.

The Aristotelian and the modern approach differ mainly not in the degree of unification nor in the nature of the correlate, but rather in the method by which this unification is brought about. In Aristotle, the association is grasped through purely subjective mental activity. Modern science unifies structure and function by a sequence

[4] Qualities are the dry, the moist, the cold, the hot. They are the necessary attributes of matter by which the latter assumes the substantiality of the four elementary bodies: earth, fire, water and air.

[5] A lengthy discussion would be required in order to establish the full meaning of the term necessity. For our purpose, it is perhaps sufficient to point out, that necessity in its contemporary as well as in its Aristotelian connotation, seems to indicate that certain occasions arise, which depend completely upon the inherent properties of matter.

of objective events which can be described in chemical terms and which depends upon the inherent properties of matter.

In conclusion, it should be pointed out that the Aristotelian unification of the structural and functional aspect of living matter made it possible to integrate the category of value into the system of science.[6] In the same way, we observe today a reconsideration of the relation of scientific facts to values.[7]

[6] . . . "We should venture on the study of every kind of animal without distaste; for each and all will reveal to us something natural and something beautiful. Absence of haphazard and conduciveness of everything to an end are to be found in Nature's works in the highest degree, and the resultant end of her generations and combinations is a form of the beautiful." (Book I, 5.-645.).

[7] Whitehead, A. N., *Science and the Modern World*, Macmillan, 1925; Köhler, W., *The Place of Value in a World of Facts*, Liveright, 1938; Gerard, R., A Biological Basis for Ethics, *Philosophy of Science*, *9*: 92, 1942; Higher Levels of Integration, *Science*, *95*: 309, 1942; Langmuir, R., Science, Common Sense and Decency, *Science*, *97*: 1, 1943.

AN EARLY RECORD OF VITAMIN-C DEFICIENCY

S. MARCOVITCH

Perhaps the earliest description of the manifestation of ill health resulting from the inadequate supply of vitamin C occurs in a treatise by Luigi Cornaro, entitled "La Vita Sobria"[1] written in 1558, nearly 400 years ago. In Addison's essays[2] we find the following tribute to Cornaro: "But the most remarkable instance of the efficacy of temperance toward the procuring of long life is what we meet with in a little book published by Luigi Cornaro the Venetian . . . Cornaro . . . was of an infirm constitution till about 40; when, by obstinately persisting in an exact course of temperance, he recovered a perfect state of health; insomuch that at fourscore he published his book, which has been translated into English under the title of 'A sure and certain method of attaining a long and healthy life.' He lived to give a third or fourth edition of it; and, after having passed his hundredth year, died without pain or agony, and like one who falls asleep. The 'Treatise'. . . is written with such a spirit of cheerfulness, religion, and good sense, as are the natural concomitants of temperance and sobriety."

After much experimentation, Cornaro restricted himself to those foods which agreed with him, these consisting of bread, the yolk of an egg, and a little meat—12 ounces in all—together with 14 ounces of wine. Cornaro observed that wine over a year old was hurtful to his stomach, but ascribed the reason to one of a mortal difficulty and hidden property of his constitution, as follows: "Every year, from the beginning of July and throughout the whole of August, I cannot drink any kind of wine soever, be it of what variety of grape or of what country it may be; for, during the whole of those two months, wine besides being very unfriendly to my palate, disagrees with my

[1] *The Art of Living Long.* Cornaro, Luigi. Milwaukee. William F. Buttler. 1917.

[2] *The Spectator.* Addison, Joseph. October 13, 1711.

stomach. So that, being without my milk,—for wine is truly the milk of the aged,—I am left without anything to drink; for waters in whatever way they may be doctored or prepared have not the virtue of wine, and fail to relieve me. My stomach becomes very much disordered, and I can eat but very little in consequence. This scarcity of food and lack of wine reduces me, by the latter part of August, to a condition of extreme mortal weakness. Neither does strong chicken broth nor any other remedy benefit me in the least; so that, through weakness alone,—not by any ailment,—I am brought very near a dying condition. It was evident to my visitors [doctors] that, if the new wine, which I am always careful to have ready every year by the beginning of September, were not then forthcoming, the delay would be the cause of my death.

" But they were yet more amazed at the fact that this new wine should have power to restore, in two or three days, the strength of which the old wine had deprived me—a thing of which they had themselves been eye-witnesses, and which could not be believed except by those who have seen it."

One wishes that Cornaro had presented more details, but enough is given to be of great interest to students of nutrition and gerontology. What is there about the new wine that enabled Cornaro to live to be over a hundred years? Only a short time ago this question would have been an enigma; but in the light of the modern vitamin research a satisfactory answer appears possible.

Considering Cornaro's greatly restricted diet, it is all the more remarkable that he managed to live as long as he did. Judged from a vitamin standpoint, the egg, bread, and meat furnished A, B complex, and G. The only possible source of vitamin C is the 14 ounces of wine, which is none too good and in fact a poor source. Kramer and Satterfield [8] report that only fresh grape juice or wine contains an appreciable amount of ascorbic acid and that in wines a year old there was none, indicating the gradual loss of the vitamin with storage.

The anorexia from which Cornaro suffered during July and August is characteristic of vitamin-C deficiency and mild scurvy, so

[8] Kramer, M., and Satterfield, G. H. 1942. Ascorbic acid content of four varieties of wines. *Food Research*, Vol. 7: 127.

that at times all he could swallow was the yolk of an egg. Since carbohydrates create a demand for vitamin C that is not made by proteins or fats, it is of interest that Cornaro selected the yolk of egg to tide him over until the new wine became available. Cornaro thus showed himself to be a keen observer and a student of himself, not only by restricting his food intake during the periods of vitamin-C deficiency but by the selection of the most suitable food on those occasions.

MEDICO-HISTORICAL NEWS AND ACTIVITIES

CONSTITUENT SOCIETIES

New York Society for Medical History, New York.

The New York Society for Medical History held its first meeting of the year on September 30, 1943, at the New York Academy of Medicine, Professor Arturo Castiglioni presiding. Dr. Henry E. Sigerist spoke on "Russian Medicine Past and Present." Dr. Arthur E. Chace reported on the medical observations he made during his trip to Russia with Ambassador Davies, and Professor V. V. Lebedenko, Soviet representative of the Red Cross in Washington, gave a warm address in Russian that was translated by Dr. Gregory Zilboorg.

NATIONAL NEWS

New Haven, Connecticut.

Through the generosity of Mr. Elisha H. Cooper of New Britain, Conn., a room adjoining the Historical Library of Yale University School of Medicine will be furnished as a memorial to the late Dr. Walter R. Steiner of Hartford. It will contain medical history items given to the library by Dr. Steiner during his lifetime and by his sisters from his collection after his death, and other Yale medical memorabilia. The room will be used as a student reading room. Dr. Steiner and Mr. Cooper were classmates at Yale, graduating in 1892.

Medical Library Association.

We would like to draw the attention of our readers to the July number of the *Bulletin of the Medical Library Association* that has been issued as a very attractive Vesalius Number, with articles by Prof. Arturo Castiglioni, Max H. Fisch, Tom Jones, and Henry S. Francis.

NEWS FROM LATIN AMERICA

Argentina.

A new issue of the *Revista Argentina de Historia de la Medicina* (Año II, No. II, May 1943) has just been received. It contains the following articles:

Juan Ramon Beltran: Enseñanza práctica de la Materia Médica, propiciada por el Dr. Juan Madera en 1828.

Juan N. Corpas: El viejo Hospital de San Juan de Dios, de Bogotá.

Plinio Olinto: Austregesilo.

Aurelia E. Alonso: La Magia de la Historia de la Medicina.

Fernando E. Catalano: Evolución histórica de la sierra como instrumento de cirugia.

Peru.

The *Anales de la Sociedad Peruana de Historia de la Medicina*, vol. 4, 1943, have been received. Fasciculus I contains the following articles:

Las Labores de la Sociedad Peruana de Historia de la Medicina en 1941-1942.

Daniel Mackehenie: Verruga Peruana, Fiebre de la Oroya, Enfermedad de Carrión o Bartonellosis Carriónica. Historia de un concepto.

Carlos Enrique Paz Soldán: La Solemne Sesión de 13 de agosto conmemorativa del Nacimiento de Unanue.

Tobías Bravo: Recuerdos de José Sanchís Banús.

Carlos Enrique Paz Soldán: Isáac Newton y los Albores de la Escuela Médica Peruana.

José Marroquín: Historia de la Orden Hospitalaria de San Juan de Dios, de Puno.

Fasciculus II is devoted to the life and works of Dr. Miguel Tafur, the collaborator of Unanue, by Dr. Juan B. Lastres.

An account of the work of the Sociedad Peruana de Historia de la Medicina for the year 1942-1943 has just been published by Dr. Carlos Enrique Paz Soldán.

NEWS FROM EUROPE

Switzerland.

The annual meeting of the Swiss Society of the History of Medicine and Science was held on August 30, 1942, at Sion in connection with the Annual Meeting of the Swiss Society of Natural Sciences. The following papers were presented, abstracts of which are published in *Actes de la Société Helvétique des Sciences Naturelles*, 122e Session annuelle, Aarau, 1942, pp. 166-175:

1. Rolin Wavre (Geneva): Galilée et le problème du temps.
2. Hubert Erhard (Munich): Über Campanellas Beziehung zu Galilei.
3. Hubert Erhard (Munich): Biologisches in Campanellas "Sonnenstaat."

4. Jacob M. Schneider (Altstätten): Thomas v. Aquin und die Hochscholastik als Vorläufer zu Kopernikus und Galilei.
5. Erich Hintzsche (Bern): Das Medizinische Institut in Bern 1797 bis 1805.
6. G. Senn (Basle): Die griechische Tanne und der boeotische Helm.
7. Jean Olivier (Geneva): Le Dr. Gaspard Vieusseux (Genève, 1746-1814). Le méningite cérébro-spinale. Le syndrome Vieusseux-Wallenberg.

We are very pleased to hear that the Swiss Society of the History of Medicine and Science intends to publish a quarterly journal that will be issued under the title *Gesnerus*.

EDITOR'S NOTE

In order to relieve the congestion of the *Bulletin* the editor felt obliged to revive the old project of publishing *Supplements to the Bulletin of the History of Medicine*. Since it was impossible, however, to secure a number of subscribers large enough to finance this new series, and since the Institute of the History of Medicine cannot publish it at a deficit, *Supplements* will be issued at irregular intervals and only when financial support can be secured for individual numbers.

The purpose of these *Supplements* is to make studies available in print that are too long for the *Bulletin* but not long enough to be published as independent monographs. Each *Supplement* will be an independent pamphlet which will be sold individually. Members of the American Association of the History of Medicine and other subscribers to the *Bulletin* will be able to purchase them at a reduced price. Standing orders for the whole series should be addressed to the Johns Hopkins Press, Homewood, Baltimore, 18, Md.

The following *Supplements* have been issued or in course of publication:

No. 1. Ludwig Edelstein, The Hippocratic Oath: Text, Translation and Interpretation. Baltimore: The Johns Hopkins Press, 1943, vii + 64 pages, 4to, $1.25; for subscribers to the Bulletin of the History of Medicine $1.00.

No. 2. Walter Pagel, The Religious and Philosophical Aspects of Van Helmont's Science and Medicine. Baltimore: The Johns Hopkins Press, 1943 [*in press*].

C. B. BROWN. *The Contribution of Greek to English.* With special attention to medical and other scientific terms. Vanderbilt University Press, 1942. xiii + 310 pp. $2.50.

Ever since the decline of classical education in the 19th century voices have been raised deploring the lack of knowledge of Greek and Latin among students. As regards medicine, Virchow's inaugural address as "Rektor" of the University of Berlin is one of the symptomatic manifestations of this counterattack; another is Harvey Cushing's memorable speech on "The Humanizing of Science."[1] If, in spite of such fervent pleas, the state of affairs has not improved during the past few years, one cannot blame those whose task it is to supply the material for self-instruction or for teaching. They have been exceedingly generous in publishing books, pamphlets and articles; almost every year has brought one or two important contributions. Naturally most of these studies deal only incidentally with medical terminology. W. R. Agard, *Medical Greek and Latin at a Glance*, and M. Spilman, *Medical Latin and Greek*, are especially valuable publications among those that concern medicine in particular.[2] And now Brown's book on *The Contribution of Greek to English* has appeared with a companion volume *The Contribution of Latin to English* to be issued "at an early date" (Foreword).

The way in which Brown proceeds is peculiar. Unlike Agard and Spilman he does not give rules for detecting the constituents of the composition of terms, nor does he collect and explain the ancient stems that occur most frequently, or the prefixes and suffixes that are important in the coinage of English expressions. Instead he presents "the words of Greek origin among the 100,000 English words of most common use" (p. ix). The Greek phrases in English transliteration are alphabetically listed; their derivatives are added with special attention—as the title of the book already points out—to medical and scientific terminology, the scientific terms "usually [having] been separated from the general terms by a black line" (p. x). Thus the book, or rather the dictionary, above all is a means of self-teaching. It is addressed to "those adventurers in the realm of words who have devoted time to the perusal of the dictionary" and "are well aware of the fascina-

[1] Cf. *Science*, LXXXI, 1935, pp. 137 ff. Virchow's address is quoted at some length by A. Rose, *Medical Greek*, 1908, pp. 23 ff. His book, interesting though a bit eccentric, gives much information about the *pro* and *con* in the discussion concerning classical languages and medical terminology.

[2] The former book has been published by Paul B. Hoeber, New York, 1937, the latter by the University of Utah, Salt Lake City, 1941.

tion of word study" (p. ix). I have no doubt that whoever is willing and energetic enough zealously to study the five sections into which the whole is divided (A-D; E-K; L-O; P-R; S-Z), will acquire an extensive and all-serviceable stock of words. The author is quite right in saying that "one's vocabulary can be effectively enlarged by attacking systematically one particular set of words at a time" (p. ix). But not only the student to whom the book is primarily directed can profit by it. For the teacher of medical Greek it provides a storehouse of information from which to draw examples illustrating the influence of Greek on common and scholarly language. Brown's work is indeed a very helpful supplement to the books of Agard and Spilman.

The value of a certain familiarity with the classical background of modern terminology is defined in the Foreword by Dean John Pomfret in the following words: "Lack of knowledge of Greek and Latin roots has hampered the mastery of the scientific terminology, and, tragically, has actually impeded the rate of progress in scientific training. Knowledge of Greek and Latin roots should make the content of science infinitely more meaningful for the student." I sympathize with so cautious a formulation. Some commendations of the usefulness of linguistic studies for the scientist sound as if they had been written by Realists of the Middle Ages. One believes he hears the old battle cry: Nisi enim nomen scieris, cognitio rerum perdit. And one feels therefore almost compelled to go to the other extreme and answer with the war whoop of the Nominalists of the past: Rem tene, verba sequentur. Probably one does better to leave the fight between nominalism and realism to the philosophers to decide. Knowledge of the ancient roots of modern terms is first of all demanded by certain educational ideals. It is the pride of the craftsman, the artist, the scholar, but also of every cultured person, to understand the tools which he uses, and language is a tool of the scientist as much as are his instruments. But the understanding of the scientific vocabulary affords another additional advantage which is rarely emphasized. Concepts are not mere images of objects. They are the reflections of observation and of thinking, the amalgamation of facts and of philosophical and scientific attitudes inherent in the human subject who views the object. Throughout the centuries of scientific progress people employed Greek and Latin roots as vehicles of expression, but they did so in an ever changing spirit. If the interpretation of Greek and Latin words does not stop at descrying the ancient stems of modern terms, if the attempt is made through the medium of words to grasp the thought that was instrumental in shaping the words, then mastery over the vocabulary will help one to understand the history of science as well as the history of men. Knowledge of words will thus contribute to humanizing science in the sense in which Osler and Cushing wanted science to be human, they and all the others for whom there is no gulf between "The old humanities and the new science."

LUDWIG EDELSTEIN.

P. O. KRISTELLER. *The Philosophy of Marsilio Ficino.* Translated into English by Virginia Conant. New York: Columbia University Press, 1943. xiv + 441 pp. $4.50.

To the historian of medicine, Ficino is the author of the *De Vita* in which he defends the value of astrology for medical treatment. To the philologist and to the historian in general, Ficino primarily is the translator and interpreter of Plato and Plotinus. Kristeller, in choosing as the central figure of his book the philosopher Ficino, draws attention to an aspect of Ficino's accomplishments that so far has been considered rarely, or at any rate hardly with the exactness and scrupulousness that it deserves.

Since Ficino never outlined his philosophical views in detail nor even expressed them independent of his exegesis of the doctrines of others, it is Kristeller's main task to elicit Ficino's philosophy from a multitude of pertinent utterances scattered throughout his various treatises. Certainly nobody is better prepared to attempt such an undertaking than Kristeller, the editor of some of Ficino's writings;[1] for few scholars would be equally familiar with the work of the founder of the Florentine Academy. Nor could the interpretation of the material assembled easily be surpassed. Being aware of the methodological difficulties involved in his enterprise (Part I, ch. 1) Kristeller carefully and minutely analyzes the essential theories of Ficino: his ontological concepts, his logical principles (Part II), his idea of internal ascent and its fundamental importance for the system as a whole (Part III). This discussion which comprises the bulk of the book is interspersed with quotations from Ficino's essays that are little known, and this ample documentation greatly contributes to making the picture drawn impressive and illuminating. Thus it is perhaps for the first time that the intricacies of Ficino's thought can be fully grasped and appreciated.

That the philosophy evolved by Ficino is essentially Platonic, Kristeller of course does not question. But he ascribes to Ficino a genuine remodelling of Platonism, he sees in him a philosopher "in his own right" (p. 3). I do not agree with the distinction which in this connection Kristeller makes between the "independence" and the "originality" of a philosophical thinker (p. 5). Yet, I admit that even if one considers Ficino a lesser philosopher than does Kristeller, one may still claim that he understood Plato in a way peculiarly his own. Serious doubt arises only when Kristeller calls Ficino "the first philosopher of the Italian Renaissance" in so far as he attempted "to express the new ideas of the Humanists in a strictly speculative metaphysical form" (pp. 12-13). Is it really possible to regard Ficino as the representative of what one might justly define as "new" in the Humanism of the 15th century?

[1] *Supplementum Ficinianum*, 2 vols., Florence, 1937.

Certainly, Ficino's faith in astrology was less revolutionary than was Pico della Mirandola's courageous rejection of astrology as a fetter of human freedom and dignity. Nor was Ficino's insistence on contemplation as the highest realization of human nature as novel as was Valla's contention that pleasure is the motive and goal of man's endeavor. Even Ficino's conviction that philosophy and Christian religion were identical, though shared by many of the early humanists, was not a dogma conceived in the truly "modern" spirit. Far more progressive than Ficino was Pletho who envisaged a natural religion, different from Christianity but in agreement with philosophy; it was in this form that the coinciding of religious and philosophical truth was generally upheld by later philosophers. The implicit presupposition of such an assumption was the criticism of the Christian dogma inaugurated by Machiavelli, but entirely foreign to Ficino, who devoutly submitted to the doctrines of the Church. Machiavelli, Pico, Valla and Pletho were contemporaries of Ficino. In my opinion it is their views rather than those of Ficino which are indicative of the new trends of the Renaissance; their works, not those of Ficino, show what men at that time dared to think and soon dared to do.[2]

Finally, on the evidence of Ficino's own words in which he calls his doctrine and his school "a resurrection of the ancient Academy" (p. 22), Kristeller dubs the Platonism of Ficino a "rebirth" of Platonic philosophy, not an "imitation" (pp. 22-23). Ficino's system, he says, was "really conceived as a genuine renaissance of Platonism," it is "not a philosophical conception that just happened to appear during the period of the Renaissance, it is, so to speak, the Renaissance become philosophical—in other words, the philosophical expression and manifestation of its leading idea" (p. 23). Such a creative revival of the past no doubt would be more in line with the character of the Renaissance than a slavish copying of the ancient authors. But if the self-testimony of a philosopher is to be taken into account at all in the appreciation of his accomplishments, did not the same Ficino who spoke of the resurrection of Platonism also assert: Nolim Marsilianam doctrinam opponere Platonicae?[3] On the other hand, on the basis of the content of Ficino's philosophy, is it justifiable even to claim that Ficino "combined the historical ideas of the Renaissance and those of the Middle Ages" (p. 29)? The philosophical attitude of the Renaissance seems typified in the pantheistic monism of such men as Giordano Bruno, a theory which is determined by "Bejahung des Lebens, der Natur und der Welt."[4] It is true, Ficino like other contemporaries of his believed psychic

[2] For a characterization of the various personalities and trends here referred to, cf. W. Dilthey, Weltanschauung und Analyse des Menschen seit Renaissance und Reformation, *Gesammelte Schriften*, II, 1923, esp. pp. 23-24; 27; 45 ff.; 149.

[3] Cf. J. E. Erdmann, *Grundriss der Geschichte der Philosophie*, I, 1866, p. 504; cf. also Kristeller, pp. 24 ff.

[4] Cf. again Dilthey, *op. cit.*, p. 284.

forces to be immanent in nature, and this view is an earlier though imperfect formulation of the Renaissance doctrine of immanence. But how far apart are the heroic enthusiasm of Bruno and the internal ascent of the soul, its separation from the body which is praised by Ficino; the this-worldliness of Renaissance philosophy and the other-worldliness of Ficino's system in which nature ranks lower than reason; the newly discovered concept of man as an autonomous being and Ficino's insistence that man is dependent on God.[8] Of course, I do not mean to deny that Ficino was also influenced by the new spirit that pervaded his time and his generation, nor do I wish to dispute the contention that his ideas in many respects form an important link in the development that led from Cusanus' philosophy to that of Bruno. Fundamentally, however, Ficino was still spellbound by the thought of the Middle Ages rather than by that of the Renaissance; he was looking back to what had passed rather than forward to what was to come.

Convincing as I find the interpretation which Kristeller has given of Ficino's philosophical system, I cannot help disagreeing with his evaluation of Ficino's rôle in the Humanist and Renaissance movements. I realize that there is a certain injustice in emphasizing this point so strongly, for within the book under review the problem of Ficino's historical position is only one among many. Yet, the question of how to place Ficino in the history of philosophy is of great general importance, and the stress laid upon it here may therefore be excusable.

LUDWIG EDELSTEIN.

EDUARD FUETER. *Geschichte der exakten Wissenschaften in der Schweizerischen Aufklärung (1680-1780)*. Veröffentlichungen der Schweizerischen Gesellschaft für Geschichte der Medizin und der Naturwissenschaften, vol. XII. Aarau-Leipzig: H. R. Sauerländer, 1941. 336 pp., 11 illustrations.

Switzerland is a very small country covering an area of only 15,944 square miles. It is poorly endowed by nature. One fourth of its territory is unfit for cultivation, unfit for human habitation. It has no mineral resources, no access to the sea, no colonies. Its population of 4.2 millions speak four different languages and an infinity of dialects. And yet in spite of, or perhaps because of these handicaps, Switzerland succeeded in becoming a very prosperous and in many ways a very advanced country. The average per capita income is high, and wealth is more evenly distributed than in other

[8] In these statements I have partly followed E. Cassirer, *Individuum und Kosmos in der Philosophie der Renaissance, Studien d. Bibliothek Warburg*, X, 1927, especially pp. 103; 65 ff.

countries. There are no slums in the cities; health conditions are good, educational standards high, social legislation progressive.

Because the soil was poor, people always had to work hard and had to use inventiveness in order to make a living. And love of their soil developed in them a fanatic sense of independence and a readiness to fight for it that kept them free for six and a half centuries in the midst of all the vicissitudes of Europe. The common heritage created a bond between the Swiss that proved to be stronger than those of race, language, or religion.

Because the country had no raw materials, the people at all times were forced to deal and trade with foreign lands. The volume of foreign trade per capita of the population is greater in Switzerland than in any other country. Located in the centre of Western Europe at the source of the great rivers of the continent, Switzerland was by nature destined to be an open country, the bridge between north and south, between east and west, economically and culturally.

Cultural influences converged in Switzerland and spread from there. In the Middle Ages, flourishing Benedictine abbeys such as St. Gall were centres of learning of international importance. In the Renaissance, the printing presses of Basle attracted scholars like Erasmus and Vesalius, artists like Holbein. Through the Swiss presses, the new learning was spread all over Europe. And in the reformation of the Church, Switzerland, through Zwingli and Calvin, exerted a far-reaching influence.

The present book discusses an aspect of Swiss civilization that is perhaps not so commonly known, namely its contribution to the exact sciences during the period of the enlightenment. Eduard Fueter, a historian and mathematician by training and today the most active historian of science of the younger generation in Switzerland, was ideally qualified for the task and has produced an extremely valuable book. It consists of two parts of which the first discusses the historical development and the many factors that have contributed to it, while the second analyzes the contribution to the various disciplines. It is really astonishing what an outburst of scientists there was in that small country during the short period of one century. One Basle family alone, the Bernoulli, produced eight mathematicians, astronomers and physicists of European reputation. Leonhard Euler, a citizen of Basle also, was soon called to the Academy of Science of St. Petersburg. A new edition of his works in 45 volumes has been in course of publication since 1911, promoted by the Swiss Association for the Advancement of Science.

At the end of the book, Fueter has a list of Swiss scientists indicating their memberships in foreign academies. It is significant to find that during that period, 51 Swiss scientists were members of the Prussian Academy of Science, 46 of the French Academy, 30 of the Royal Society, and 24 of the Academy in St. Petersburg.

All sections of Switzerland took part in that development, and while the exact sciences flourished, biology had such representatives as Haller, Bonnet, Zimmermann, Tissot, and others. It was a great century during which the ideas were conceived and the discoveries made from which the 19th century was to reap the fruits.

With its extensive notes and bibliography, Fueter's book is a mine of information that every historian of science will consult with great benefit.

HENRY E. SIGERIST.

ROBERT P. PARSONS. *Trail to Light. A Biography of Dr. Joseph Goldberger.* Indianapolis and New York: The Bobbs-Merrill Company, 1943. $3.00.

By enlarging man's knowledge and control of his environment and his own life, medical research has definite implications for social institutions. An obvious and direct social implication is in relation to nutrition. This is evident in the present widespread interest in food problems, which stems ultimately from the research work of the last thirty years, the discovery of vitamins and the later investigations of mineral and protein requirements.

Among the fundamental contributions to this field the work of Joseph Goldberger on pellagra will always rank prominently. It was Goldberger and his associates who by their detailed and time-consuming experiments offered convincing proof of the dietary origin of pellagra. The story of his thorough and exhaustive research is engrossingly related by Dr. Parsons in his biography of Goldberger.

Born of Jewish parents in the Carpathian section of Hungary, Goldberger came to the United States while still a child and grew up on the New York East Side during the eighties and nineties of the last century. As a boy he showed scholastic promise and was enabled by his parents to spent two years in the study of engineering at the College of the City of New York. At the end of this period, however, he switched to medicine and convinced his parents to put him through the three year medical course at Bellevue Hospital Medical College. Graduation was followed by eighteen months of internship and two years of increasingly successful practice at Wilkes-Barre, Pa. But medical practice failed to satisfy Joseph Goldberger. At the instigation of his friend William Dean, he applied for a position with the U. S. Public Health Service and received an appointment. Here he came into his true element, and for thirty years he engaged in investigations of typhoid, yellow fever, dengue, typhus, diphtheria, culminating finally in his fundamental studies on pellagra. In a sense his career symbolizes the development of medicine during this period, from the heyday of bacteriology to the era of vitamins and deficiency diseases. It is indeed symbolic that Goldberger, who throughout his career

as an investigator had been engaged in studying bacterial and virus diseases, made his greatest contribution by elucidating a nutritional deficiency disease.

Dr. Parsons gives an interesting and even thrilling account of Goldberger's work. He is at his best when describing his subject's scientific researches (Chapters IV-XV). Attention must be called, however, to certain historical inaccuracies and several other weak points that mar the book as a whole.

In his brief sketch of the history of typhus, Dr. Parsons mentions that the first classical dissertations on this disease were provided by Fracastorius and Cardonus (page 200). The latter name should be Cardanus.

Later he says that the German government sent "Rudolph Virchow from Würzburg" to investigate the typhus epidemic in Upper Silesia, and also that Virchow was so stirred by the plight of the weavers of Silesia "that he launched . . . into many recommendations of social reform which, being regarded as dangerously radical by the government, cost him his chair at the university for several years" (page 204). This is incorrect. When Virchow went to Silesia he held an appointment at Berlin. He did not go to Würzburg until after he had been driven from his position at Berlin. Furthermore, his appointment at Würzburg came immediately after his dismissal at Berlin.

On page 313 Dr. Parsons speaks of Casimir Funk as a German. This is an inaccuracy. Funk is a Polish Jew.

In addition to these errors the first two chapters are marred by certain weaknesses that apparently arise from the author's lack of understanding of the cultural milieu in which Joseph Goldberger grew up. For instance, within the first eight pages of the first chapter there are four references to *matzoth* and to *gefüllte* fish as having been sold in the grocery store conducted by Goldberger's father (pages 17, 19, 21, 24, 39). These references have apparently been inserted to create local color, but they demonstrate the author's ignorance of the Jewish background. It is very unlikely that matzoth would be sold to such an extent as to require four references in the text, except at the Passover season, and there is no indication that this is the case. The references to *gefüllte* fish are likewise absurd. This dish is prepared in the home. No self-respecting Jewish housewife would buy it in a grocery store, and it is unlikely that it was sold in the elder Goldberger's store. Dr. Parsons would have been better advised to speak of herrings.

In another passage (pages 38-39) Dr. Parsons attempts to explain Goldberger's high scholastic standing. He discounts Mrs. Goldberger's explanation in terms of heredity and environment (Joseph's maternal grandfather was an eminent Hebrew scholar in Hungary) and concludes: "The best explanation is that he had a quick and perceptive mind, from childhood he had had a prodigious bump of curiosity, and as a youth he had taken a

genuine interest in his studies." Obviously, this explanation is simply an elaborate tautologism which might have been expressed more simply in the statement that Joseph was a smart boy. There is a grain of truth, however, in the explanation ventured by Goldberger's mother. Learning has always been venerated among the Jews; indeed, the scholar was held in higher esteem than the wealthy man among the Jews of Eastern Europe. This is illustrated in the efforts made by Goldberger's parents to enable him to study in privacy (page 41). Furthermore, the tradition of scholarship brought to America by Goldberger's parents undoubtedly influenced his development (pages 19-20). Doctor Parsons notes these statements and facts, but is apparently unaware of their significance and so does not utilize them in explaining the development of Joseph Goldberger.

In connection with this criticism it will be well also to note that we are told very little about the parents and other relatives (brothers and sisters) of Goldberger. For example, on page 32 a stepbrother Jacob suddenly appears and we are left in the dark as to the precise relationship between him and Goldberger. Dr. Parsons might have thrown more light on Joseph Goldberger had he told us more about his family and their cultural background.

Finally, in a number of passages Dr. Parsons records thoughts that are supposed to have passed through Goldberger's mind and also conversations that occurred between him and other persons. It would be interesting to know whether these are based upon materials contained in Goldberger's sea-chest or whether they are the products of Dr. Parsons' imagination.

Despite these criticisms, we wish to repeat that the book as a whole is an engrossing account of the work of an outstanding American doctor.

GEORGE ROSEN.

ALICE HAMILTON. *Exploring the Dangerous Trades. The Autobiography of Alice Hamilton, M. D.* With illustrations by Norah Hamilton. Boston: Little, Brown and Company, 1943. 433 pages, 9 pl. $3.00.

Miss Hamilton carefully avoids any hint concerning her age, but *Who's Who* reveals that she was born in 1869. She tells in detail about her happy but uneventful youth as the daughter of a Presbyterian business man in Indiana. She studied medicine at Ann Arbor and did post-graduate work in Leipzig, Munich, and in the newly opened Johns Hopkins Medical School. All these places are delightfully described. Dr. Hamilton then became a teacher of bacteriology at the Woman's Medical School of Northwestern University. At Chicago she became connected with Hull House and Jane Addams, and this connection gave the direction and strong social inspiration to all her subsequent work.

In 1910, at an age when other people's careers usually are well defined, Alice Hamilton began what was to become her real life work: exploring dangerous trades, a work which has given her an outstanding place not only in the annals of American medicine, but of international medicine, as the American pioneer in this field. She started with a survey of the lead industry in Illinois. She then made a national survey for the Federal Government on the same subject. Surveys for the Federal Government in the war industries of World War I, on airhammer damages, poisoning from copper, carbon monoxide, anilin dyes, and mercury followed. Dr. Hamilton (meanwhile having become Prof. Hamilton of Harvard) then investigated fatigue, the wool industry, solvents, carbon disulphide. For anyone who has had only an inkling of industrial medicine, this list shows what really superhuman labor Alice Hamilton has performed. She gives very vivid descriptions of these enquiries, which offer to the student and layman a fair introduction into industrial medicine and a good record of labor conditions twenty years ago.

Having studied in Germany and having visited the country again in 1915, 1919, 1933 and 1938, Miss Hamilton adds to the purely medical side of her book very interesting and fair sidelights on what may be called "politics" in a higher sense of the word. The same may be said of her memories of her visit to Russia for the League of Nations in 1924, of the Sacco and Vanzetti case, of her excursion on birth control. The book ends as it starts, with an idyll: the author's retirement to the Connecticut countryside.

This is a highly interesting and very well written book although its tenor is sometimes not as one might expect from a pioneer; not tough, but rather too sweet and nice when one visualizes its object. We can learn from it a great deal about industrial medicine and the social history of the first quarter of the 20th century—and almost nothing of the author's character.

ERWIN H. ACKERKNECHT.

Past and Present Trends in the Tuberculosis Movement. A Symposium of Historical Papers presented at the 38th Annual Meeting in Philadelphia, Pennsylvania, of the National Tuberculosis Association. Historical Series No. 1. Preprinted from the *Transactions of the 38th Annual Meeting*, 1942, 47 pp.

DOROTHY WHITE NICOLSON. *Twenty Years of Medical Research.* National Tuberculosis Association, 1943, 97 pp.

The first American tuberculosis association was founded in Philadelphia in 1892, and in order to celebrate its fiftieth anniversary, the National Tuberculosis Association held its 38th Annual Meeting in that city and

presented a symposium of historical papers prepared by the Association's *Committee on Archives.*

This Committee on Archives of which Prof. Richard H. Shryock is chairman and Dr. Robert G. Paterson, secretary is likely to become the Association's most important committee, namely the one that will survive all others. Indeed, fifty years from now there should be nothing left of the National Tuberculosis Association but its archives and a committee to administer them, because by that time tuberculosis should have disappeared from the United States.

I can visualize America's physicians meeting in Philadelphia in 1992 to commemorate the foundation of the first tuberculosis association and to celebrate the overcoming of the white plague. All papers will be historical. They will discuss how the standard of living rose, how American cities were rebuilt whereby slums were eradicated ruthlessly, how social discrimination ceased so that negroes could share the white man's standards. They will point out that all pregnant women, whether rich or poor, are examined once every month, are free from work with full wages two months before and two months after delivery, and bring their children to life in maternity homes. They will mention the fact that miners are no longer permitted to work more than six hours underground, that they have frequent periodic examinations and every year four weeks vacation with pay. And finally they will discuss how the National Tuberculosis Association, taking advantage of all these social and economic factors, cooperating with medical centres and government agencies, mobilizing the entire population in this fight, was able to develop a program that combined medical and social measures enabling one to find incipient cases, to cure them and to rehabilitate the former patients so that the once dreaded disease at long last was forced to yield.

All this sounds very Utopian, and yet are we not all striving to create these very conditions? And when we read the historical papers presented at the Philadelphia symposium of 1942 and realize how much progress has already been achieved, the eradication of tuberculosis in this country within half a century is anything but Utopian.

Jabez H. Elliott, whose untimely death is deplored by tuberculosis specialists and historians alike, discussed *The Problem of Tuberculosis Prior to 1880* showing how confused views were before Koch's discovery and what a terrific toll of life the disease took. It has been estimated that in London in the 17th and 18th centuries, 15 to 25 per cent. of all deaths were due to consumption, and in 1857 when registration of deaths became general in Great Britain, the mortality was still 325 per 100,000. It decreased steadily, a fact which at that time can hardly be attributed to medicine but rather to the rising standard of living. The general death rate was dropping also.

Robert G. Paterson in a short paper packed full of facts reviews *The*

Tuberculosis Movement in the United States of America 1882-1904. The period indeed was an important one beginning with Koch's discovery and leading to the foundation of the National Tuberculosis Association. It established the basic methods which were so successfully applied on a large scale in the following period under the leadership of the National Tuberculosis Association, the history of which is briefly reviewed by Charles J. Hatfield.

The Association was founded in June 1904 in Atlantic City. Its first secretary was Henry Barton Jacobs of Baltimore whose minutes of the first meeting are famous for their accuracy and completeness. It is perhaps not generally known that Dr. Jacobs' priceless tuberculosis collection is now in the Welch Medical Library of Johns Hopkins. It is not only rich in books and pamphlets but contains also a collection of autograph letters of Robert Koch, scrapbooks and newspaper clippings on tuberculosis. The catalogue that we hope to publish soon will probably be one of the most complete historical bibliographies on the subject.

The fourth paper by Esmond R. Long discusses *Modern Trends in the Understanding and Control of Tuberculosis.* It is a review of progress and is permeated with the enthusiasm and optimism without which no crusaders are made.

With an introductory paper by Richard H. Shryock in which the social historian views the tuberculosis movement from the broad perspective of history, the pamphlet is a valuable contribution, of great interest to physicians, historians and laymen.

In the beginning the activities of the National Tuberculosis Association were chiefly devoted to educational work but in 1916 already the suggestion was made that a fund should be raised for research. Plans were postponed on account of the war. In 1917 the *American Review of Tuberculosis* was founded, and in 1921 the first research grant was extended. It was the beginning of a long series of grants which have greatly stimulated research and yielded rich returns.

Dorothy White Nicolson gives a fascinating review of *Twenty Years of Medical Research,* in which she discusses in simple and clear language the researches carried out under the auspices of the Association. A classified bibliography of 30 pages greatly increases the value of this publication.

Let us hope that fifty years from now one more Utopia will have become a reality. And when the time comes, the National Tuberculosis Association besides the Committee on Archives will have to establish one more continuation committee, one for the combating of tuberculosis in foreign countries. There will be countries less fortunate than ours and no medical problem can be considered as solved before it has been solved on a world-wide scale.

HENRY E. SIGERIST.

PAUL DE KRUIF. *Kaiser Wakes the Doctors.* New York: Harcourt, Brace and Company, 1943. 151 pp. $2.00.

Paul de Kruif, as everyone knows, is an enthusiast and an optimist. He loves the people, the "common man" as the slogan now goes, and would like to see everybody healthy and happy. This is the most lovable side in him and endears him to his friends. Wherever a medical discovery is being made, Paul de Kruif is on the spot and reports about it *urbi et orbi* in glowing terms, in best American slang, and not always too critically. Since he writes for "Reader's Digest" and other popular magazines, his articles are read by millions of people and have more than once raised expectations and hopes that science was not able to fulfill. He still believes that hundreds of thousands of mental patients could be cured by shock therapy which is, to say the least, more than doubtful.

Now Paul de Kruif has a new enthusiasm. He met Henry J. Kaiser, the shipbuilder, came under the spell of that powerful personality, went to the West Coast to see the health facilities of the new shipyards and the result is the present book. It is a dramatic account of the health organization that Kaiser has created for his workers and of the pioneering efforts of Dr. Sidney Garfield, his chief medical officer.

Kaiser discovered that the health and welfare of workers is important, that group medicine practised by salaried physicians through medical centres is superior to individual practice, and that a first-rate medical serice can be financed, including the cost of capital construction if large enough groups of people contribute 7 cents a day each in addition to the money that comes in under the Workmen's Compensation Act.

It is very important that Kaiser made this discovery because he had enough imagination to draw the necessary conclusions and had the means and the power to build an excellent health organization and to defend it against the unavoidable attacks from the part of what is commonly called "organized medicine."[1] Kaiser's health plan is a splendid demonstration of what can be done—and has not been done in most industrial undertakings of the country. It has solved the problem of medical care for the workers of his shipyards, and it is a powerful weapon to the nation in the pursuit of the war because trite as it sounds, it is pretty obvious that urgently needed ships cannot be built by disabled workers.

We must not forget, however, that Kaiser's idea is anything but new. There are countries where this very type of group medicine through medical centres has been practised very successfully for the last 25 years and on a nation-wide scale. In 1941 the Soviet Union had 13,461 medical centres in

[1] The term is very inappropriate. The A. M. A. and its constituent societies are organizations of physicians, not of medicine. One of their chief efforts is to prevent the organization of medicine.

cities and 13,512 in rural communities. In this country long before Kaiser, such doctors as Donald E. Ross and Clifford Loos did the pioneering work. They built up a health organization that serves over 85,000 people in Los Angeles on a pre-payment plan. They demonstrated what 7 cents a day and even less can do. They did it under much more difficult circumstances, at the bottom of the depression when money was scarce. Their struggle with "organized medicine" was much tougher than Kaiser's because public opinion was not prepared as it is now and because it is much more difficult for an agency to wreck a sound and needed health program in a time of great national emergency. And Ross and Loos were not alone. In every section of the country, courageous doctors were fighting a heroic battle to bring health to the people at a price they could afford. And everywhere they won the battle and their experiences laid the actuarial foundation upon which plans of the Kaiser type could be built. De Kruif mentions some of them but only incidentally.

One new feature in Kaiser's plan is that he succeeded in reconciling the doctors of the California Medical Association and that his plan became connected with California Physicians' Service. This cooperation is a result of the time factor. California Physicians' Service was organized as an ordinary limited fee-insurance system without medical centres, group medicine, salaried physicians, etc. Like similar plans in other states, it provided a periodic payment plan that made it easier for patients to pay their doctors' bills while still preserving the traditional forms of medical care with the fee-for-service remuneration dear to the medical hierarchy. When the war broke out and war industries mushroomed in California causing a tremendous influx of population, C. P. S. had the choice between two things: It could either accept the idea of medical care through medical centres, or could stay aside, let industrialists and the federal government organize medical centres for war workers and fight a losing battle against them. Very wisely it chose the first alternative, made a deal with the federal government and with Kaiser. Thus it is correct to say that Kaiser—but we must add: and the federal government—have awakened the doctors. It is important that one powerful constituent of the A. M. A. has gone a step forward. Kaiser's agreement according to which family members of workers are attended by private practitioners under the C. P. S. is far from ideal. It is a compromise solution but probably the only one that was possible with the present shortage of personnel and equipment.

Paul de Kruif's fallacy begins, in my opinion, when he assumes that voluntary plans of the Kaiser type, built and operated without any public funds can be extended to the entire country and represent a solution of our health problem. I believe this to be a fallacy because it is based on the two following assumptions: 1) that all industrialists will be as intelligent as Henry Kaiser, and 2) that the present period of economic boom will last forever.

What we have seen in other war plants is far from encouraging. The lack of appreciation of health problems, the lack of intelligence, foresight and courage from the part of most industrial leaders has been simply appalling. Medical conditions in many industrial areas are outrageous, and when the Government was ready to put up considerable funds in order to remedy some of the worst abuses, the slightest objection from the part of "organized medicine" was enough to wreck plans. In Baltimore, we need not go far to find examples. There is a natural alliance between most industrialists and the hierarchy of the A. M. A. because they are both fighting to preserve the world of yesterday and it is hard to see how our industrial leaders should suddenly accept the visions of Henry Kaiser.

Today we have a war economy which is a planned economy. There is no question of markets. Whatever can be produced is sold before it is made. But what about tomorrow? Shall we continue to produce under a planned economy, planned for peace-time needs, or shall we go back to the "good old days" of free enterprise, free competition and economic anarchy? From all symptoms it seems very likely that we shall decide for the latter alternative. Then we shall have other crises, depressions and mass-unemployment. But if the unemployed cannot pay 7 cents a day, who is going to look after their health? Who is going to run their medical centres? I suppose that in such a case we shall have to call on the Government "bureaucrats" that we have elected in a democratic way.

What I found very irritating in Paul de Kruif's book is his constant use of the words "generosity" and "mercy." What generosity is there in building up a health plan that benefits all, employer, employees, physicians, and the nation alike and is financed with the nickles and dimes of the workers themselves? Why not speak of "common sense"? I am quite convinced that Kaiser is not motivated by selfish purposes and that he takes a genuine interest in the welfare of his workers. There have been such employers ever since the time of Robert Owens. And as to "medical mercy," I think that in a civilized society every individual who through his labor contributes to the welfare of his fellow men has a right to all means available for the protection of his health. This is not a question of mercy.

It is gratifying that Kaiser has not only awakened the California doctors but also medical reporters like Paul de Kruif. In a candid introductory chapter he confesses that so far he was interested chiefly in scientific medical progress. Kaiser stirred him and he came to realize that scientific progress is wasted unless it can be applied on a mass scale, for the benefit of the people. In studying the Kaiser plan he, for the first time, fully appreciated the significance of the nefarious "invisible hand" that reaches out from Chicago wherever doctors are fighting a gallant battle to protect the people's health.

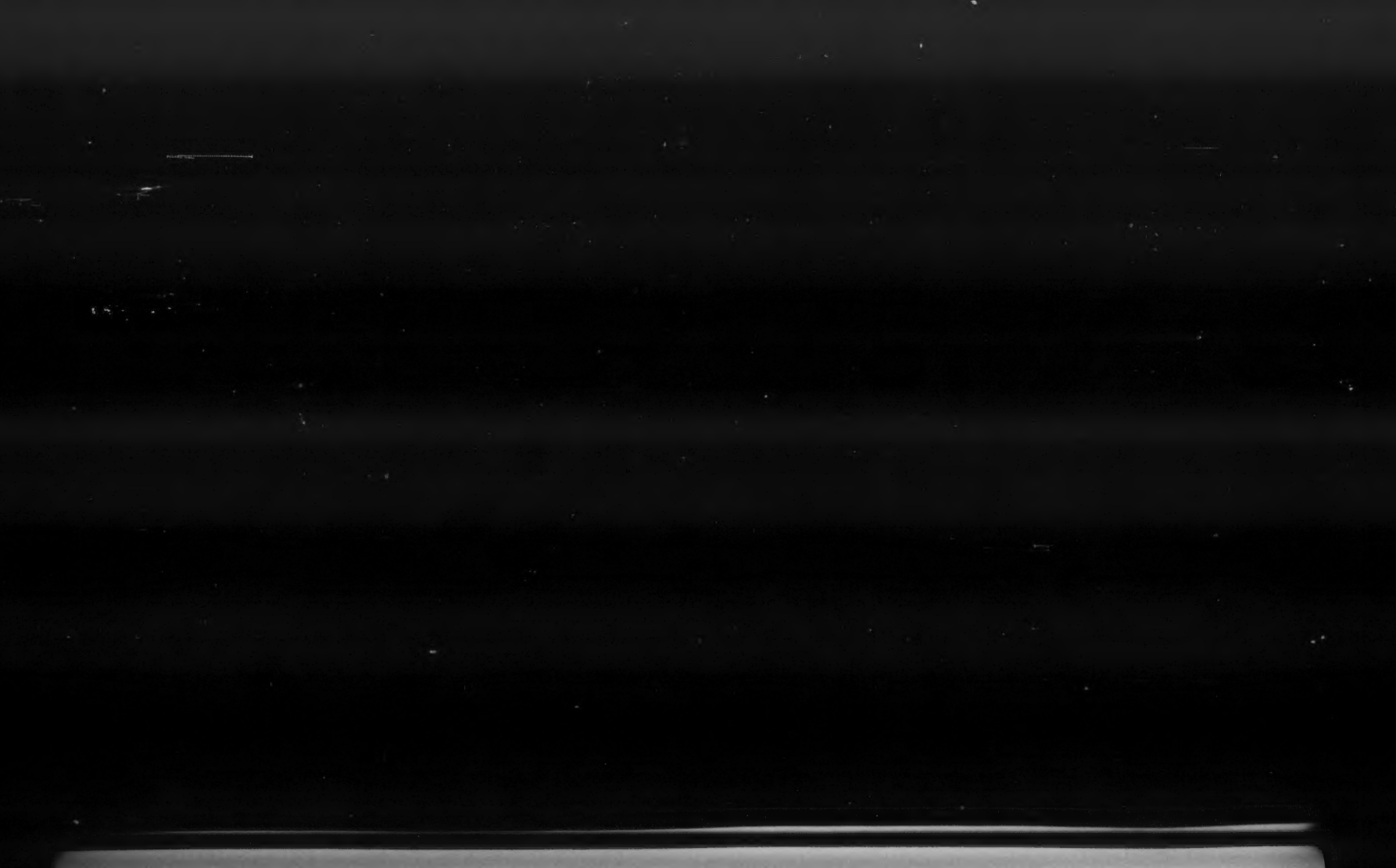
The trouble with Paul de Kruif is the same as with most other journal-

ists. He does not study enough. He writes emotionally on the basis of observations and impressions. If he took the trouble to study problems more thoroughly, his words would carry infinitely greater weight. But we like him anyway for his honesty, for his enthusiasm and his optimism.

HENRY E. SIGERIST

History of the Reading Hospital. Published by the Board of Managers on Occasion of the 75th Anniversary of the Reading Hospital, December 9, 1942. Reading, Pa.: The Reading Hospital, Inc., 1942. 287 pp. Illustrated.

When in 1867 a group of physicians from this growing city in eastern Pennsylvania united to organize the Reading Dispensary to treat the indigent sick of their community, they founded an institution which progressively kept apace with the times and expanded into the modern hospital with its various departments and nursing school. In 1886 the Dispensary became a general hospital and moved into a new building, especially constructed for the purpose; this in turn was soon outgrown, and in 1926 the present buildings, patterned after Mannheim Hospital in Germany, were occupied. Throughout its existence the institution has depended for financial assistance upon private philanthropy and contributions of the townspeople.

This volume includes a careful account of the growth of the hospital, giving proper credit to those who made it possible; a historical description of the various departments, the nursing school, and the Ladies Auxiliaries; biographical sketches of deceased physicians and board members; and a list with personal data of physicians and board members to the present time. Reading's proximity to Philadelphia makes it self-evident that many of the features of the hospital were inspired by Philadelphia institutions and physicians. Future historians of American hospitals will find such volumes as this of great value in outlining the patterns which American cities followed in providing care for their sick inhabitants.

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